
PATHOLOGY
of the HEART

The heart of man is noble

(Second Edition)

PATHOLOGY *of the* **HEART**

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To My Wife

Foreword

THIS NEW EDITION, as was anticipated from the welcome afforded the first edition, gives ample evidence of the high regard in which the book is held by the profession as a whole and that large component devoted to the study of heart disease. The first edition exemplified a broad approach to the subject in that embryology, normal anatomy and histology as well as physiology and etiology were combined with pathologic anatomy, pathologic physiology and clinical manifestations so as to constitute a unified consideration of current knowledge and of research potential. The same breadth of approach prevails in this new edition. Pathology, in its maturity, continues to grow and develop.

It has been necessary to reset the type completely which adds to the exceptional opportunity for revision by those who contributed to the earlier edition. This situation has been exploited in many ways, such as in sentence and paragraph structure, certain changes in classification and terminology, insertion of new illustrations, alteration of paragraph headings and extension of bibliography. It is fortunate indeed that the original authors are available for the revision, and the enthusiasm of their response is exemplary. A certain amount of alteration has been necessary to harmonize the presentation with new chapters. The use of somewhat smaller type is not a conspicuous change and the book can be read as comfortably as ever.

New chapters expand the overall coverage admirably. The wisdom of the choice of topics is complemented by the selection of contributors known to be recognized authorities in their fields. Catholicity is evident throughout but we may be proud that a group of Americans can write a book of this character. And each new chapter continues the fine tradition of the earlier edition. These follow the methods of the preceding edition in discussion of form and function, of clinical manifestations and diagnosis and of prognosis and therapy.

The chapter on conduction system clearly delineates widely accepted views and presents fairly and adequately the few controversial aspects. The pathology of the aorta is now described sequentially and in a manner readily available for reference. A comprehensive presentation of histochemical procedures is a great value to any pathologist and is well adapted to the special study of the cardiovascular system. In the course of becoming a spectacular adjunct to the treatment of acquired and congenital lesions of the heart, surgery has compelled the pathologist to give special and often instructive attention to the various correctible conditions. The methods, usefulness and limitations of surgical attack are admirably described. The influence of heart disease on other organs and systems of the body has been recognized for a long time and has been carefully studied. Only comparatively recently has the interdependence of cardiac and pulmonary function been firmly established. To have this relationship so well covered that all students of disease in the thorax may profit is a fine addition to the book.

An impressive perspective of the whole subject is provided by the historical review, with amplification in individual chapters, and the suggested avenues for further study and research. The editor and contributors are to be congratulated on a task well done.

HOWARD T. KARSNER, M.D., LL.D.

Preface

THE COLLABORATORS of this monograph on the heart deeply appreciate the cordial reception by the medical public of the first edition. The call for a second edition within the space of six years indicates that the volume has filled a need. It is gratifying to have all of the collaborators of the first edition participate in the preparation of the new edition, and to note that they have done so with even greater enthusiasm.

Owing to the extensive revisions and additions that have been made, it has been necessary to reset the type completely. In addition, five new chapters have been added, covering the following subjects: the conduction system, diseases of the aorta, cardiopulmonary disease, surgery of the heart, and histochemical procedures. The emphasis has remained on correlation of the clinical and pathologic findings. In order to make room for new material included in the original chapters and for the additional chapters, and still keep the selected material within the space of one volume, it has been necessary to limit the space allowances sharply and to use smaller sizes of type.

Sincere thanks and appreciation are gratefully expressed to the collaborators for their splendid cooperation, to Mr. Charles C Thomas and his associates for outstanding achievement in bookmaking, to Mrs. Ruby Arquette for meticulous care in typing and proofreading; and to Mrs. Ruth Tobey for assistance in the preparation of the indices and for proofreading.

Finally, the editor offers the hope that this volume may be found useful and that it may reflect credit to the field of pathology by supplying the reader with readily available authentic information with reference to diseases of the heart.

S. E. GOULD

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PATHOLOGY
of the HEART

History of the Pathology of the Heart*

EDWARD B. KRUMBHAAR

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USEFUL KNOWLEDGE of the pathology of the heart—"pathology" including all the changes produced by disease whether structural or functional—is a relatively recent acquisition along the long path of medical history. The slowly accumulating knowledge of disordered cardiac structure and function produced little of practical value before the 19th century. The ancients even maintained that the heart was not subject to disease—*cor non aegrotare posse*, as Hippocrates is said to put it.[†] Galen's classification of types of heart disease (wounds and inflammations, pericarditis and pericardial effusions, palpitations) disregarded any logical sequence and, as might be expected, was woefully incomplete

* In the short space available, it is obvious that frequently the bare mention of a name must suffice. Fortunately, the details of important contributions—often, the pertinent portions of the original texts, in English translation—by such leaders as Benivieni, Haller, Morgagni, Vieussens, Senac, Heberden, Parry, Adams, Stokes, Cowper, Durozier, Potain, Cornigan, Hope, W. His, Jr., Keith and Flack, can be found in Willus and Keys' *Cardiac Classics*, Major's *Classic Descriptions of Disease*, and several volumes of Kelly's *Medical Classics*, and other anthologies.

† This statement is offered by both Moon and Herrick as the basis for the erroneous belief that the heart cannot be diseased. The nearest that I, with the help of W. B. McDaniel II, have come to this notion is in Littre's translation of *de Morbis: Nullus in corde morbus suboritur* (No disease arises in the heart); elsewhere it is stated that the heart does not labor with pain. It is suggested that "aegrotare" may be an early paraphrase of the original Greek, in which case Hippocrates should not be held responsible for the more glaring error.

to modern eyes. Yet it controlled the current of medical thought for some 1300 years. With very few exceptions, it was only in the 15th century that even gross anatomic changes began to be recorded. Pietro di Montagnana (died 1460), for instance, noted damaged hearts in 14 dissections at Padua.

Functional disturbances such as palpitation (said to be frequently mentioned by Hippocrates) and arrhythmia (a term attributed to Galen) were naturally recognized much earlier though the word "palpitation" until recent times covered a wide area ranging from a violent pulsation to an increased activity due to diseases. An irregular pulse meant little more than an irregular pulse until instruments of precision led to classification of the various arrhythmias into objectively recognizable types. These are considered in Chapter V, B and their story outlined later in this chapter. The two branches of the subject, structural and functional, were, to be sure, often mingled in what today would be called a clinicopathologic study, straight pathologic anatomic writing gradually emerging as knowledge of this branch became more extensive.

The development of knowledge of pathologic changes in the heart came slowly, as it did for most of the internal organs. This growth can conveniently be considered in three overlapping periods: the first, the longest and least valuable today, characterized by

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Tabula xxii. ad Observationem Lxi. cor triplici ventriculo præditum ostendit.

- A. Cor triplici præditum ventriculo.
 B. B. Duo dextri cordis ventriculi.
 C. Sinister ventriculus.
 D. Arteria pulmonaria ex utroque dextro ventriculo prodiens.

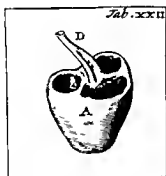


Figure I-1. From Kerckring's report (in *Spicilegium Anatomicum*, 1670, Obs. 69, Table 22), showing a heart with a third ventricle. D, Pulmonary artery arising from the double right ventricle. (The letters BB and C do not appear in the original illustration.) Note the crudity characteristic of many 17th century illustrations

isolated observations of such material as chance offered, the second, in the 17th and 18th centuries, a period of systematized collections of cases usually including some clinical material; and the third, in the 19th and 20th centuries, a period of treatises and textbooks, with increasing attention to the laws underlying the observations. Almost negligible through ancient, classical and medieval times, for practical purposes the beginning of cardiac pathology may conveniently be located in the Renaissance with Benivieni's *De Abditis Morborum Causis* (published posthumously, 1507). Of the 111 chapters in this small book, one, of the 20 that included a postmortem report, describes what seems to be an acute pericarditis, though it is not clear whether by "the cavity" *cum pilis refertum* (covered with hairs) is meant that of the pericardium or of one of the cardiac chambers. Another case revealed a "polyp of the heart," an erroneous

diagnosis that was not finally corrected until the 19th century (see Gross, 1857). However, disorders of the heart contributed through the centuries, though not as often as one would expect, to the progress of the anatomic concept of disease. Even in the great *Sepulchretum* (1679) of Bonetus, we find few significant items of cardiac pathology, though there are numerous cases of palpitation and cardiac polyps, some of the latter having been so diagnosed during life. These cardiac polyps had a history far out of proportion to their importance. Bauhin (1592), Tulp (1641), famed for his Rembrandt's Lesson in Anatomy, and Malpighi (*De Polypo Cordis*, 1686) were others who prolonged the confusion between ante- and postmortem clots, until Kerckring (1640-1693) showed that the red, easily removable kind was merely a postmortem clot (*Spicilegium Anatomicum*, Obs. 73, 1670). The error was gradually eliminated as the gray, tightly adherent ante-mortem thrombus became differentiated from the loose red variety. Even in 1839, in the first edition of Gross' well known *Elements of Pathological Anat-*



Figure I-2. Giovanni Battista Morgagni (1682-1771), by Angelica Kauffmann. (From Castiglioni's *Storia di Medicina*.)



Figure 1-3 Raymond Vieussens (1641-1715). (Reproduced by courtesy of Oxford University Press)

omy, polyps appeared as "polypous concretions," though in the third edition (1857) "polypous" was changed to "fibrinous." Kerckring also was an early contributor to the pathology of congenital heart disease; his 69th observation showed an infant's heart with a large double right ventricle (*cor triplici ventriculo*) and a pulmonary artery leading from each, to fuse later, as is clearly shown in Figure 1-1.

In the 17th century the custom of publishing assembled cases, from the literature as well as from personal observation, reached its highest development in Bonetus' *Sepulchretum* and then in Morgagni's great *De Sedibus et Causis Morborum* (1761), which is properly credited with having generally established the anatomic concept of disease. The *Sepulchretum*, though it included 2934 observations (cases) made by 470 authors, reports very little about the heart. Even Morgagni's *De Sedibus* contains much less about the heart than about other organs and systems. However, we find reports of the structural changes in a case of what was soon to be called angina pectoris; one of the earliest accounts of ap-

parent heart block (slow pulse with syncopal attacks), cases of vegetative endocarditis—one associated with gonorrhea; a case of rupture of the heart; one of myocardial degeneration; and one of congenital hypoplasia of the aorta,—other names of course being applied to most of these. Morgagni (Figure 1-2) had the great merit of correlating careful clinical study with necropsy findings better than any of his predecessors and, for that matter, than many of his successors. One of the greatest medical figures of the 18th century, he deserves a prominent position in the history of the pathology of the heart.

Systematic descriptions of cardiac pathology, though of course not in any way comparable to those in modern texts, had occasionally appeared between the time of Benivieni and that of Morgagni. We think of four, all by prominent physicians—Fernel, Vieussens, Lancisi, Senac. Jean Fernel (1497-1558), a humanist who pursued all branches of human knowledge, conceived of a *Universa Medicina* which he never finished. In one of the three completed sections, *Pathologia*, he grouped heart diseases under the peculiar headings of inflammation, crsipelas, *tumores contra naturam*, ulcers and wounds. Over a century later, Raymond Vieussens (Figure 1-3) produced his *Traité Nouveau de la Structure et des Causes des Mouvements du Cœur* (1715),* which has been called "the first to make serious contributions to our knowledge of diseases of the heart" (Moon). In addition to good anatomic descriptions of such items as the course of the coronary vessels and the valve in the coronary sinus, he described mitral stenosis (see Figure 1-4) and the characteristic pulse of aortic regurgitation. (See also under Endocardium, page 17.) His contemporary, Giovanni Maria Lancisi (1654-1720, Figure 1-5), for 13 years a Professor of Anatomy, while practicing all the while, became the greatest clinician in Italy. Important contributions to cardiovascular knowledge are to be found in both his celebrated books, *De Subitaneis Mortibus* (1707), and *De Motu*

* Published the year before his death, this text is extremely rare. In the catalogues of several great medical libraries it is only to be found concealed as Part 1 of his *Oeuvres Françaises* (1715).

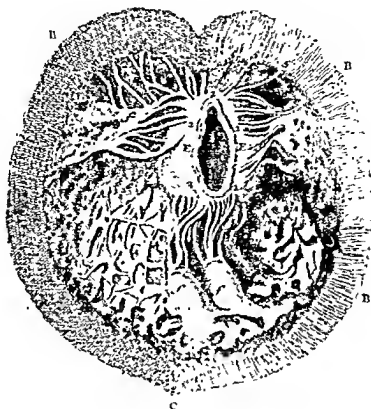


Figure 1-4 Vissens' illustration of a stenosed mitral valve from his *Traité Nouveau de la Structure et des Causes du Mouvement Naturel du Cœur* (Toulouse, 1715). (From Major's *History of Medicine*, courtesy of Charles C Thomas.)

Cordis et Aneurysmatibus (published posthumously, 1728). He recognized heart disease as one of the common causes of sudden death and gave good descriptions of sclerotic and of warty valves and of the coronary system. (See Figure 1-6.) He also described some arteries that were furnished with narrower orifices (*nugustioribus orificiis praediti sunt*). He dwelt at some length on cardiac "aneurysms" (in the strict etymologic sense of dilatation, a meaning still used for some aneurysms). Hence for him, aneurysm was commoner in the atrium than in the ventricle and least common in the left ventricle. His handling of the causes of heart disease in general was less successful, stressing congenital defects, violent emotions, physical effort, palpitations. The causes of cardiac hypertrophy hit somewhat nearer the mark: heredity, leaky valves, calcified arteries and valves, chronic asthma, true and false and syphilitic aneurysms. His contemporary, I. F. Albertini (1662-1746) favored heredity and syphilis (using mercury in its

treatment) as major causes of heart disease, and correlated dyspnea and pulmonary edema with it.

De la Structure du Cœur, de son Action et ses Maladies (1749) by Jean Baptiste Senac (1693-1770; Figure 1-7) has been generally accepted as the most important extensive early work devoted entirely to the heart. In the chapters on the diseases of the heart he recognized inflammation of all three of its layers, and noted that pericarditis might follow pneumonia or pleurisy or infectious fevers; he also observed pulsation of the arteries of the neck when the left ventricle was enlarged and pulsation of the cervical veins when the right ventricle was enlarged (Major, *History of Medicine*, 1954, p. 633). Ossified coronaries and insufficient valves were other valuable observations. He included discussion of tumors, abscesses, "ulcers" and wounds, as well as arrhythmia, palpitation and syncope (weak action) of the heart. However, many of his descriptions, like those of his contemporaries,



Figure 1-5 Giovanni Maria Lancisi (1654-1720). From an engraving by Sebastian Conca in the first edition of his *De Motu Cordis et Aneurysmatibus*, 1728. (Courtesy of Armed Forces Medical Library.)

are found in an atmosphere of such fanciful concepts that they make no great impression on the modern reader.

Textbooks of pathology, in the sense in which we use the word "textbook" today, may be said to have started modestly with Matthew Baillie's (1761-1823) 52-page work, *The Morbid Anatomy of Some of the Most Important Parts of the Human Body* (1793). In the 24 pages of the chapters on the heart and pericardium, he touches briefly on inflammation, abscess, gangrene, polyp, cardiac aneurysm, fibrous, bony, and "earthy" thickening of the valves, rupture of valves and myocardium, malformations and hypertrophy of the heart; and on "white spots," inflammation, adhesions, dropsy, excessive dryness, and scrofulous tumors of the pericardium. Clinical notes were included in the first edition only in the German translation. The early textbooks in France and Germany, such as Lobstein's *Traité d'Anatomie Pathologique* (1829) and the younger Johann Friedrich Meckel's *Hand-*

buch (1812, 1818) dealt with general pathology only, the special pathology being covered by atlases. On the other hand, the first textbook of any size in this country, *Elements of Pathological Anatomy* (1839), by Samuel D. Gross (1805-1884), was divided, as most teaching texts are today, into general and specialized pathologic anatomy. But in the latter portion, the heart and its membranes occupied only 40 of the 510 pages. Rupture of the heart was regarded by Gross, and for most of a century after, as "generally the result of ulceration or of the softening of fatty degeneration."

The French School, dominant in the early 19th century because of the political situation in Europe and the French achievements in physical diagnosis, also set the pattern in the expanding knowledge of the pathology of the heart. (See Figure 1-8.) Two great clinicians, Jean Nicholas Corvisart (Figure 1-9) and R. T. H. Laennec (Figure 1-10), led this advance. Corvisart's *Essai sur les Maladies et les Lésions Organiques du Cœur* (1806), by means of clinical lectures with a pathologic

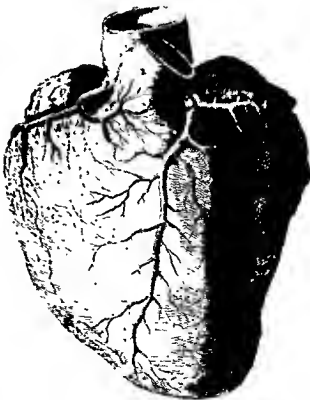


Figure 1-6. Vieussens' illustration of the coronary arteries from the *Traité Nouveau*, Plate 5, anterior view. (Courtesy of Armed Forces Medical Library.)



Figure 1-7. Jean Baptiste Senac (1693-1770) (From Herneck's *History of Cardiology*, courtesy of Charles C Thomas.)

basis, established our present custom of considering heart disease according to its three layers (pericardium, myocardium and endocardium) with a fourth class for diseases *contra naturam* and those affecting several tissues (pancarditis). Corvisart emphasized the frequency of organic heart disease, separating it from functional varieties, correctly unraveled the still tangled problem of polyyps, distinguished between hypertrophy and dilatation, and between fatty infiltration and degeneration (which latter he said he had never seen), and between effects of stenosis of the different valves. He described rupture of the chordae tendineae and papillary muscles, also hydatids, as well as the conventionally accepted cardiac disorders. His pupil Laennec, in his celebrated *Traité de l'Auscultation Médiate* (1819, 1826), further developed Corvisart's lead, quoting from him frequently but with greater precision in the description of physical signs and the correlation with autopsy findings. For the first time it became possible to distinguish hypertrophy of dif-

ferent chambers. Laennec appreciated that failure of the heart was seldom seen except in dilated ventricles, with or without hypertrophy; and that a hypertrophied heart is a diseased heart. To him is ascribed the statement that a normal heart should be the size of the person's clenched fist. He recognized that communications between the ventricles were not necessarily congenital in origin. He gave good descriptions of cardiac irregularities and murmurs, but interpreted wrongly the origin of the two normal heart sounds. The occasional staining of the valves by postmortem hemolysis he attributed to inflammation.

Thereafter, the heart occupied increasing space in textbooks of pathology, and included increasingly, especially in the 20th century, more and more helpful information and lines of investigation from correlated disciplines.

At this point the story becomes so voluminous that it must be considered under special headings, and even then by taking illustrative items only. We turn first to Congenital Malformations.

Congenital Heart Disease offers good examples of a long, random progress of pathologic knowledge in a given subject before integration was accomplished. A number of congenital heart lesions had been observed and reported for centuries without coordination and utilization of the data obtained. Sometimes, as in the case of *morbus caeruleus* and the fourfold lesions of the tetralogy of Fallot, the two concepts developed independently for some time. One has only to compare the earlier accounts with their largely empiric



Figure 1-8. École de Médecine de Paris in the early 19th century, when French pathology was dominant. (From a contemporary engraving in the Bibliothèque Nationale.)



Figure I-9. Jean Nicolas Corvisart (1755-1821). Engraving by Blot from painting by Gérard. (From Major's *History of Medicine*, courtesy of Charles C Thomas.)

explanations of the genesis of the several lesions with Carl Rokitsansky's (Figure I-11) *Die Defekte der Scheidewände des Herzens* (1875) to realize the rapidity of progress made in the grasp of the subject. Recently acquired embryologic knowledge and tremendous zeal in unearthing new types of malformations were important aids thereto. Already in the third edition of his *Lehrbuch der pathologischen Anatomie* (1856), Rokitsansky had included such congenital anomalies as acardia, ectopia, two-chambered heart, three-chambered heart with either two atria or two ventricles, a rudimentary ventricular septum with aorta arising from both ventricles, several varieties of defective atrial or ventricular septum (Figure I-12), patent ductus arteriosus, double heart, bifid apex, doubled great vessels, excessive (and insufficient) number of

valve cusps. In fact, he mentioned so many varieties that he has been criticized as having slavishly included for each structure all conceivable pathologic defects. However, he was able to predict unknown varieties, examples of which were later discovered, an achievement not often to be found in medical history. This process of assembling and reinterpreting has been carried on conspicuously in the present century by Mande Abbott (1869-1940, Figure I-13).

Some of the early isolated findings were so premature that they failed to contribute to the stream of progress. Some even retarded it, as when Botallus (1565) and Cassendi (1630) used their findings of openings in the septa of some adult hearts as evidence for the normal existence of a pervious cardiac septum. Harvey, too, had seen these persisting



Figure I-10. René-Théophile-Hyacinthe Laennec (1781-1826). (From a miniature on ivory in the Faculty of Medicine of Paris.)

slits and knew that various lower species had a common ventricle throughout life, but consideration of all the evidence and logical deductions led him to the correct answer to this long-disputed problem. At the other extreme, Vieussens is said by Corvisart (1806) to have observed a premature closing of the foramen ovale in the fetus.

Ventricular septal defects are said to have been reported by observers as early as Stensen (1638-1686). Corvisart recognized simple septal defects as being either congenital anomalies or the result of inflammatory perforation. H. L. Roger (1809-1891) was able to diagnose the simple septal defect by auscultation (1879) and regarded it as an anomaly, often harmless, rather than an organic disease.

The combination of lesions known as cardiac cyanosis (*maladie bleue*, *morbus caeruleus*) has been known since the 18th century; in fact, E. Sandifort (1742-1814) of Leyden in 1777 gave a detailed description that covered its four chief lesions, as did also Morgagni (1761), William Hunter (1784), J. R. Farre (1814), E. Gintrac (1824) and T. B. Peacock (1866). However, E. L. A. Fallot's *Contribution à l'Anatomie Pathologi-*

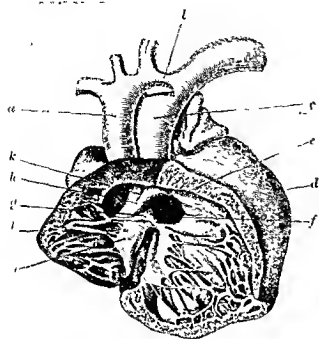
que de la Maladie Bleue (1888), appearing at a timelier moment, attracted so much attention that the condition became known as the "tetralogy of Fallot," an eponym that seems destined to endure for some time. The "Eisenmenger complex," Fallot's tetralogy without pulmonary stenosis, was first reported in 1897 (*Ztschr. f. klin. Med.*) The rare "idiopathic dilatation of the pulmonary artery" we owe to B. Zuber (1903) and B. S. Oppenheimer (*Tr. A. Am. Physicians*, 48:290, 1933).

The *ductus arteriosus* was also known as the *ductus Botalli*, though Castiglioni and others thought that Botallus had probably confused it with the foramen ovale. Aranzio saw it about 1550 (confirmed by G. Carcano, 1593; Reiman, 1757). Norman Chevers saw (1845) the first typical solitary case in an adult, confirmed at autopsy. Ligation was first suggested by J. C. Munro in 1888, but not successfully carried out until 1939 by R. E. Gross and J. P. Hubbard.

Of the heart as a whole, examples of double hearts had occasionally been observed (Zacu-



Figure I-11. Carl Rokitsansky (1804-1876). (From an original *carte de visite* photograph, College of Physicians of Philadelphia.)



a Aorta aus dem rechten Ventri. b kommen. c Lungenarterie, d linker Ventri. e Ein-atzpunkt des vorderen Septums vorne links an der Lungenarterie. f Defect. g Pars membranacea rechts an der Lungenarterie. h das von e abgezwergte Rudiment eines accessori-schen Septums, i vorderer Zipfel der Trikuspidalis, k spaltähnlicher Zugang in einem Comm-rudiment, l Isthmus aortae

Figure 1-12. Heart with transposed aorta and septal defect. (From Rokitsky's *Die Defekte der Scheidewände des Herzens*)

tus Lusitanus, 1637), as well as bifid apices and lesser abnormalities of a similar kind. Nonviable acardiac monsters and ectopia cordis are included in Andral's *Précis* (1829), as in several textbooks of the period. Baillie (1788) described true dextrocardia as part of a general transposition of viscera (*Phil. Trans. Roy. Soc. London*, 78:350, 1788), and explained it as one of the three types of deviation from the normal creative action that produces structure, the others being deficiency and redundancy. A two-chambered heart is described in Farre's book, and Peacock cites two cases, though perhaps unreliable, from the 17th century (Pozzi, 1676; Lanzoni, 1691). His examples of three-chambered hearts start with Chemineau (1699) and continue with increasing frequency up to his time. Such anomalies, amounting to different degrees of septal defects, reached their culmination in

Rokitansky's magnificent work on the subject, mentioned above, classifying 11 varieties of ventricular and eight of atrial septal defects.

The several types of congenital transposition of the great vessels were well recognized by the middle of the 19th century. Their pathogenesis, however, was but little understood. An aorta arising from both ventricles (i.e., riding on a septal defect) appears in J. R. Farre's book (1814); he cites earlier descriptions by Sandifort and by William Hunter (1784). An early description of transposition is found in Baillie's text (1797), and many more had been reported by 1870 (especially in the *Transactions of the London Pathological Society*, and other English journals). To some, the anomaly seemed "a spontaneous aberration," Peacock attributed it to faulty development of the aortic septum; Rokitsky, to a failure of the normal torsion of the aorta and pulmonary trunks. There the matter rested until Spitzer's explanation, based on the reappearance of normally suppressed phyloge-



Figure 1-13. Maude E. Abbott (1869-1940), a life-long student of and contributor to the knowledge of congenital heart disease. (Courtesy of Armed Forces Institute of Pathology.)



Figure 1-14 William Heberden (1710-1801), who first described angina pectoris (Contemporary engraving, after Sir William Beechey's portrait in the Royal College of Physicians)

netic and ontogenetic phenomena, led to the detorsion theory. In Maude Abbott's words (*Atlas of Congenital Cardiac Disease*, p. 54): "... early arrest in the bulbar region of the primitive heart tube inevitably interferes with the clockwise torsion that takes place in this region in normal growth; any such lack of torsion (i.e., detorsion) will result in the obliteration of the normal human (left) aorta, and the persistence of the reptilian right aorta which is evanescent in the human embryo but now appears in permanent form as the 'transposed' vessel."

Size of Heart. Gross variations in the size of the heart, as might be expected, early attracted attention. At one extreme, an adult heart weighing $3\frac{1}{2}$ ounces (100 Gm.) in a medium-sized woman of 40 without cardiac symptoms, was reported by Favelle (*Proc. M. and S.J., London*, 5:358, 1843), whereas at the other extreme, Senac speaks of a heart weighing 15 lb. (6.8 Kg.) which, as a weight

set down over 200 years ago, must be taken with considerable reserve. T. H. Wright of Baltimore described one weighing 5 lb., 3 oz. (2368 Gm.) in a large Negro dying of heart failure (*Am. J. M. Sc.*, 12:5, 1833). Vieussens, long before, had recognized that an enlarged heart was not compatible with perfect health. Hypertrophy of different chambers was not recognized until after the advent of a refined physical diagnosis (Corvisart, Laennec).

Lancisi appreciated that if the ventricles are dilated, the atria also will be, and that hypertrophy of the left ventricle might be accompanied by dilatation of the right side, with signs of decompensation. A hundred years later, the French school distinguished between hypertrophy of each of the four chambers and also between dilatation of each. They recognized at the autopsy table concentric hypertrophy (where the cavity is diminished in size), the much commoner hypertrophy and dilatation (Corvisart's "active aneurysm"), and simple dilatation, a thin wall with little or no change in myocardial volume (Bertin, 1833). This last Corvisart, with etymologic correctness, called "passive aneurysm." The cardiac aneurysm of our mod-



Figure 1-15. James B. Herrick (1861-1934). (Photograph by Wulinger. Courtesy of Dr. Ralph H. Major and Charles C. Thomas.)

ern parlance was called "partial dilatation"—tiresome distinctions these, but necessary to keep in mind if the earlier writings are to be comprehended properly.

Coronary Heart Disease. The story of what is today the most important of all cardiac disorders, coronary artery disease and its consequences, may be said to begin in 1768 with Heberden's (Figure 1-14) vivid picture of what he called "angina pectoris" from the sensation of strangling in the chest. He placed it in the class of spasmodic, not inflammatory, complaints. The earlier account by the Earl of Clarendon of his father's attacks with pain in the left arm also depicted angina pectoris, though the outcome in sudden death would more likely have been due to a major coronary occlusion. It was not until 1912, however, that coronary thrombosis was clearly established by J. B. Herrick (Figure 1-15) as a clinical entity, recognizable during life and not necessarily fatal. Incidentally, in Heberden's account, and he described a number of cases, the heart is mentioned but once, and then as not affected by the anginal attack; no indication has been found that he associated the pain with the heart. Coronary "ossification" (today we read *calcification*), to be sure, had been correlated with angina-like pain several times in the past, by Morgagni (1761) among others. Herrick says that Lancisi mentioned calcified coronaries as a cause of cardiac dilatation, and Senae is said to have associated them with true cardiac aneurysms (i.e., post-infarctional stretching). The great John Hunter, examining the heart of Fothergill's patient who had angina pectoris (1776), found that the two coronaries "were become as one piece of bone," but the connection between the attacks of pain and the condition of the coronaries was not considered. When Hunter himself died (1793) in an anginal attack, his coronaries appeared as open bony tubes. To Jenner and Parry (*Syncope Anginosa*, 1799) belongs the distinction of first attributing the chest pain to disease of the coronary arteries. Parry also glimpsed a causal relation between myocardial ischemia and the anginal attacks. Allen Burns (*Diseases of the Heart*, 1809) produced pain in the leg by ob-

structing the circulation and suggested that this might also be the mechanism causing the pain in the heart. The same line was followed (1927-1932) by Thomas Lewis when he demonstrated that sharp pain was induced by exercising muscle deprived of its normal blood supply.

Those who are puzzled as to why practical comprehension of coronary disease at the bedside should have had to await the discoveries of the 20th century should read Herrick's description of the various events that account for this gap: a mixture composed of true observations that had to be rediscovered, errors typical of our halting medical progress, false theories that led seekers astray, wrongly evaluated experiments, over-reliance on the long dominant method of physical diagnosis, and the authoritative but erroneous views of Rokitsky and Virchow, together with a number of misleading designations for causes and effects (such as cardiac neurosis and fatty de-



Figure 1-16. Karl Albert Ludwig Aschoff (1866-1912). (Photograph taken in the autopsy room of the Philadelphia General Hospital, 1920.)

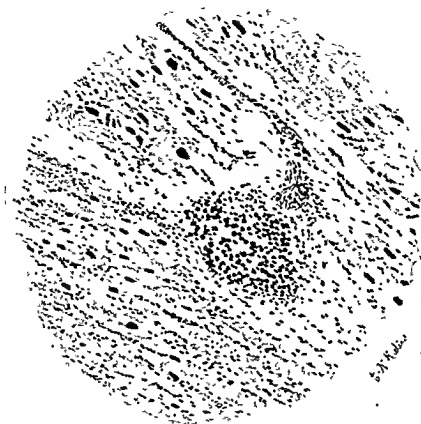


Figure 1-17. An early illustration of an Aschoff body. (From second edition of Aschoff's *Pathologische Anatomie*, 1911.)

generation). In the field of etiology and pathogenesis, understanding of myocardial infarction and rupture necessarily had to wait for comprehension of the concepts of thrombosis and embolism (Virchow, 1846) and necrosis (Weigert, 1880). The parts played by coronary stenosis without occlusion and by coronary spasm in relation to precordial pain, ranging from simple pain to the classic picture of angina pectoris, cannot yet be satisfactorily explained, even at autopsy, in many borderline cases.

Cardiac Rupture. Rupture of the myocardium has been known for at least 300 years, Harvey having found at autopsy a tear in the left ventricle, presumably in an infarcted area (1647). Morgagni reported several similar tears and is said to have died of one himself. Its predisposing cause, however, was generally thought until some 30 years ago, to be fatty degeneration of the heart muscle (see Krumbhaar and Crowell, *Am. J. M. Sc.*, 130:1828,

1925), this error being ascribable to the pre-microscopic authority of Richard Quain (1850). It persisted for many years, however, notwithstanding Elleaume's (*Paris thesis*, 1857) insistence on the dominating role of the coronary lesions and Weigert's clear exposition of the necrotic nature of the softened muscle (1880). The ancients' belief that traumatic injuries of the heart were necessarily fatal persisted to the end of the 19th century, in spite of numerous reports in the literature to the contrary. Gould and Pyle (1937) devoted several pages to this subject.

Rheumatic Heart Disease. A connection between acute articular rheumatism (rheumatic fever) and heart disease was not even suspected until the end of the 18th century. This connection between a joint disorder and what was for more than a century the most important of heart diseases seems to have first appeared in print in the second edition of Baillie's *Morbid Anatomy* (1797). This idea

Die erwähnten Knötchen sind außerordentlich klein, höchstens submiliar, und entstehen durch Zusammenlagerung auffallend großer Elemente mit einem oder mehreren abnorm großen, leicht eingekerbten oder polymorphen Kernen. Die Zusammenlagerung der Zellen erfolgt oft in Form eines Fachers oder einer Rosette. Die Peripherie wird von den großen Kernen, das Centrum von dem oft zu einer schwächeren oder anders färbbaren aussehend nekrotischen Masse zusammenfließenden Protoplasma der Zellen gebildet. Bei flüchtiger Betrachtung erinnern die fächerförmigen Herde an kleinste Gichtnekrosen mit peripherem Zellmantel, wie man sie häufig in Gichtnieren findet. In den rheumatischen Knötchen handelt es sich aber nicht um tuberkulöse oder Fremdkörperriesenzellen mit mehreren regelmäßig geformten Kernen, sondern um Gebilde, die mehr an die großkernigen Elemente in gewissen Sarkomen oder in pseudoleukämischen Wucherungen erinnern. Allerdings bestehen die Knötchen nicht ausschließlich aus solchen großkernigen Zellen, sondern kleine und große Lymphocyten, auch polymorphkernige Leukocyten schließen sich wenigstens in der Peripherie zwischen die großen Zellen ein oder bilden eine periphere Zone, von der unregelmäßige Ausläufer sich weithin in das Bindegewebssepten erstrecken.

Figure I-18. Aschoff's original description of the specific "Knötchen," from his communication in *Verhandlungen der deutschen pathologischen Gesellschaft*, 8 51, 1904.

he got from his patient, Dr. David Pitcairn, who had mentioned it in his clinical lectures (1788). Jenner also reported, to the Fleece Medical Society, on a "Disease of the Heart following Acute Rheumatism," but this was not published, and his manuscript was never found. This correlation was accepted by British physicians (W. C. Wells, 1812; Hawkins's *Gulstonian lectures*, 1826), but such was the predominance of French medicine at that time that Bouillaud is usually credited with establishing this relationship regarding "the fibrous tissue of the heart" (1835). A myocardial connection, as might be expected, came gradually and considerably later. Myocardial "induration" was an ancient concept which obviously included fibrosis from various causes as well as from acute rheumatic fever. It was not until Ludwig Aschoff (Figure I-16) in 1904 described, in addition to diffuse interstitial changes, the characteristic nodule (Figures I-17 and I-18) which bears his name that this most important of the three heart layers definitively entered the rheumatic picture. Without the aid of the Aschoff nodule, diagnosis of diffuse myocarditis of rheumatic origin is still often uncertain, and "nonrheumatic" myocarditis still appears in textbooks to cover various conditions of well- or ill-defined etiology—usually the latter. It is noteworthy, too, that for this, the most important of all

infectious diseases of the heart, the problem of its etiology and pathogenesis still remains unsettled. For some years there has been increasing acceptance of a connection with streptococci—some say hemolytic, some non-hemolytic. Menzer's suggestion (1902) that an allergic response of the tissues was responsible is the most widely supported, notwithstanding numerous objectors.

Cardiac Syphilis. Syphilis, which until recent years constituted the third of a great triad of cardiac disorders, has now, thanks to better prophylaxis and to penicillin, been relegated to a position of minor importance. Knowledge of cardiac syphilis was acquired more slowly than in the case of syphilis of other viscera. Proksch (*Die Geschichte der venerischen Krankheiten*, Bonn, 1895) and others attribute much of this delay to the authoritative John Hunter's conception of gonorrhea and syphilis as one disease. Syphilitic lesions of the heart were identifiable only with difficulty and uncertainty before the discovery of *Treponema pallidum* and the acquisition of more intimate knowledge of the microscopic changes characteristic of the disease. Syphilitic pericarditis and mural endocarditis are now regarded as practically nonexistent, except rarely by extension from the adjacent myocardium and root of the aorta. Narrowing of the coronary ostia, by syphilitic

aortitis, was early described by Jakob, who on one occasion found complete closure of the right coronary artery without loss of detectible functional capacity (*Erlangen Dissertation*, 1891). Cardiac lesions in persons with syphilis, to be sure, had been recorded from the time of Paré and Lancisi, but without indication as to whether the lesions themselves were syphilitic. In the myocardium, an early well authenticated example of syphilis is a gumma of the septum of a heart deposited in the Pennsylvania Hospital Museum in 1879. This was examined in 1907 by G. C. Robinson (*Bull. Ayer Clin. Lab.*, No. 4, 1908), who, by correlating it with the patient's history and the record of a pulse rate of 30 beats per minute and lower, established the earliest verified example of heart block caused by gumma. That syphilis could cause both gummatous and diffuse interstitial changes in the myocardium was established by Virchow (1858). Both varieties have been thought to be rare by almost everyone but Warthin (1914), who believed that the diffuse variety was common even in adults, that it had a specific microscopic picture and that not infrequently treponemata could be demonstrated.

Pericardium. Senac, who devoted 30 pages to diseases of the pericardium, was familiar with the shaggy acute and indurated chronic inflammations, some of the latter apparently tuberculous, others of rheumatic origin. He was not the earliest to be acquainted with pericardial hydrops which sometimes produces "a monstrous dilatation," and he recognized that the sac might also contain blood, air or pus. He cited two pericardial "tumors" found by Calen (a cystic tumor in a monkey and a scirrhous in a rooster), but we may well be skeptical as to their neoplastic nature, as was Senac himself of Calen's conjecture that they might occur in man. Tumors and cysts had also been reported by Bonetus. Senac regarded abscesses and ulcers of the pericardium, some undoubtedly tuberculous, as common. Senac recounts descriptions by Lower, Vieussens, Lancisi, Haller and others of adhesions, often apparently complete, of the two pericardial layers, and adds two cases of his own one in which "the two ventricles were

adherent in three or four places" and a second in which the apex was attached by a short stout band. Senac curtly dismisses the report of "three green stones" found in the cavity by Lancisi as insignificant and merely as adding to the number of rare diseases; "*taches blanches*," on the other hand, he found to be common. "Stone" or "ossified" hearts had been described by various early writers before Senac; though obviously, without the aid of the microscope, the composition of the hardened masses remains in doubt. Haller's case, in a young man, with associated similar changes in the valves would today suggest a rheumatic origin (Figure 1-19). Allusion has already been made to the importance of the English school in establishing the connection between heart disease and rheumatism. On etiology and pathogenesis, as is to be expected, Senac is far weaker, though he did recognize pneumonia and pleurisy and other infections as frequent causes of pericarditis. Little more was added to the knowledge of pericardial diseases until developments in cellular pathology made possible more exact identification of tuberculosis, secondary neoplasms, and other conditions, and until bacteriology elucidated much of their etiology. It is evident that the constrictive element of chronic adhesive pericarditis was recognized by Lower (1669), by Lancisi, and by Morgagni (1761), in one of his cases. The condition was overlooked, however, for more than a century, in spite of the clear descriptions by Chevers (1842), Criesinger (1854, recorded in 1856), Wilks (1670) and Kussmaul (1873). It was not until 1896 that Friedel Pick's article on pericarditic pseudocirrhosis brought general recognition of this variant; a condition which, regardless of its etiology, was important because of its prognostic individuality and because it was soon to be demonstrated as amenable to surgical relief (see Beck, 1931-1935). Pericarditis as a complication of myocardial infarct was recognized by C. Bäumlér (1672) and V. Vernig (1892), but not well appreciated before M. Sternberg's description of *Pericarditis episthenocardica* (1910).

Endocardium. Examples of diseased valves

like those of other parts already mentioned, accumulated at first sporadically, along with the gradual establishment of the anatomic concept of disease. A lesion of the tricuspid, the most resistant valve of the four, was one of the earliest described—by Lower (as cited by Bonetus but not found in the *Tractatus de Corde*), and by Senac (who cites Haller and several others, Vol. 2, p. 403, 1789 edition). Senac, however, recognized that the semi-lunar valves were more frequently involved than the "auricular." Thickening and incompetency of the aortic valves was well described and illustrated by Cowper (1706) and by several of the British school a century later, among others Hodgkin (1828) and Corrigan (1832) who had an especially good compre-

hension of its functional results as is worthily perpetuated in "Corrigan's pulse." Mitral stenosis was known to Vieussens (1715) who also recognized a resultant dilatation of the left atrium with a small, weak pulse, damming of blood in the lungs and hypertrophy of the chambers of the right side.

The concept of endocarditis, even the name itself, is ascribed to J. B. Bouillaud (1796-1881; Figure 1-20), whose *Traité Clinique des Maladies du Cœur* (1835) gave a much clearer picture of the disease than had hitherto existed. However, this falls far short of Trouseau's extravagant statement that it was "a description to which nothing could be added." Bouillaud considered three stages: a period of congestion with swelling and softening and

OPUSCULA

OBSERVATIO LII

Lapis in corde (h).

Sed meretur imprimis enormis morbus postleris memorari, quo egregius juvenis haud ita dudum exstinctus est. Matre natus, ut ex medico clinico percepi, obnoxia palpitationibus cordis, ante octo annos, ephēbus tunc, in simile malum incidit. Ipse ea die vocatus, quā interitū, absque pulsu, quem in carpo tangeres, reperi, ut tamen carotides vehementer subsilirent. Frigido jam sudore madentem tristi prognostico invitus reliqui. Paulo post exstinctum corpus aperuimus. Pericardium cordis, pulmo pleurae passim adnatus, & in tota superficie pericardii passim scirrhī albi, alii duri, alii alba materie puris simili pleni fuerunt. Eorum scirrhorum ope cor cum pericardio uniebatur, irresolubili omnino vinculo. Ventrīculi dextri pars inferior femilipidea, calculi tephacei ex arenalis congesti ope cum pericardio cohaesit. Sinus inter duas membranas valvularum aortae callosi & partim lipidici fuerunt. In valvulis aortae inter membranas materies fibulosa erat, tendines

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dines vero, qui eas valvulas retinent, postea denique & osses squamulis varii reperti sunt. Sed praecipuum malum in valvulis venae pulmonalis latuit. Ex tota durissima & solidissima fuerunt, ita calculosa materie plene, ut passim dissectis fibris creparent. Sinus etiam pulmonalis caro lipidosa materie fida fuit. Neque cor, neque vasa magna molem solitam exceperunt. Raritatem nulli ipsa res viginti annorum auit. Non clausum autem huius juvenis cor; neque latus apertum, caruit alterna requie, sine qua ne ipsum cor quidem esse potest. Nam simulter ventriculus, & aggre sanguinem a sinu sui lateris recipiebat, & in ipsa contractione sua per hiatus immutabilem officinarum valvularum mitralium remittebat ad eum sinum. Ita ex aorta pariter sanguis inter inexplicabiles rigidisque valvulis aortae in cor redire potuit. Unde, cum cor perpetuo stimuletur, palpitavit perpetuo, & cum cerebro sanguinis latus mittere non posset, eiusmodi soporis causa fuit, qualem ex defectu cruoris, a venae sectione & a vulneribus feritus ingruit.



Figure I-20. Jean-Baptiste Bouillaud (1796-1881). (From an original *carte de visite* photograph at College of Physicians of Philadelphia.)

ulcération or suppuration, a second stage of thickening, fibrous plaques, adhesions and firm "vegetations," and a third stage of endocardial induration with calcification and ossification, with or without valvular stenosis. This third stage, which is easy enough to see, was known for over a century, as has just been described. The first, in part recalling the congestive beginning of any inflammation, was largely theoretic yet persisted into 20th-century teaching, while the ulceration clearly indicates a malignant form, "as the ancients would have called it" (Bouillaud). Bouillaud's second stage, that of organization, aims none too clearly at an intermediate stage between the acute and chronic stages, which has been thought to indicate in that pre-bacterial era an acquaintance with subacute bacterial endocarditis.

Acute endocarditis was first clearly differentiated at a considerably later period. In 1852, some years after the publication of Bouillaud's *Traité*, W. S. Kirkes, the brilliant English pathologist, had given a clear picture of vegetations being washed off the heart

valves to block blood vessels with fibrinous material, some with pyemic-like symptoms. Isolated examples of both kinds were reported sporadically, but without general recognition until Sir Samuel Wilk's (Figure I-21) publication in 1868 of *Pyemia as a Result of Endocarditis*. Our present term, "acute bacterial endocarditis," followed isolation of methods for identifying bacteria. The splitting off of the much commoner subacute bacterial endocarditis (*endocarditis lenta*) was established on the basis of its slower course and its frequent association with streptococci (viridans and nonhemolytic). Recognition of this variety owes much to H. Schottmüller, and in America to Osler and E. Libman, who stressed its regular occurrence on previously damaged tissue and its slow, almost invariably fatal termination, a condition now happily changed by antibiotic drugs. Consideration of the more recently described endocarditis of lupus erythematosus disseminatus and "atypical verrucous endocarditis" of Libman-Sacks (1924) may be found in various places in Chapter X of this book.

Myocardium. Lesions of the myocardium, being in general less striking than those of the other two cardiac layers, took longer to be recognized and classified adequately. Its importance, however, has been appreciated for more than a century: "It is in the vital and anatomical condition of the muscular fibers that we find the key to cardiac pathology," in the words of William Stokes (1804-1878), the distinguished Irish physician who described Cheyne-Stokes respiration and the syndrome of heart block. It took the manpower needs of the first world war and the persistent acumen of Sir James Mackenzie (Figure I-22) to force the realization that valve murmurs in themselves were significant only when accompanied by limitation of the functional capacity of the myocardium.

Of the localized lesions of the heart muscle, cases of abscess and ulcer had been rather vaguely described from Bonetus on, and this cause is still carried "on the books" as a cause of rupture. Laennec cites Bonetus (*Sepulchretum*, Bk. 2, Sect. I, Obs. 86), Morgagni and Senac as having collected many cases of ulcer

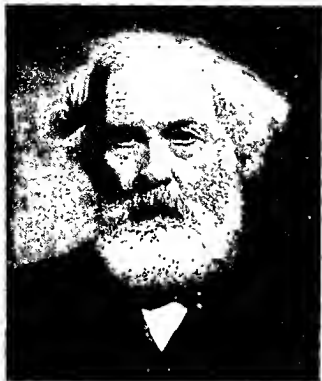


Figure I-21. Sir Samuel Wilks (1824-1911). (From the collection of the Armed Forces Medical Library.)

of the interior surface, his single example caused rupture of the ventricle—"a very rare accident almost always the result of ulceration of the ventricular parietes." True fatty degeneration, in the sense of "an actual transformation of the muscular substance into a substance possessing most of the chemical and physical properties of fat" was recognized by Laennec, though only "in a small portion of the heart at one time." Without the aid of the microscope, he had to rely on such crude evidence as the appearance of a spot of grease on a piece of folded paper within which suspect muscle had been compressed. He distinguished this condition from "simple softening" (the myomalacia of Ziegler) and never found rupture attributable to it, though the gross similarity of fatty degeneration and necrosis led to the former being wrongly regarded as an important cause of rupture until well into the 20th century. (See earlier discussion under Cardiac Rupture.)

Myocarditis, a term used by Sobernheim in 1837, was recognized as being either acute or chronic—the former category doing well enough for the suppurative forms and even

for the nonsuppurative forms, after microscopic criteria for inflammation had been established. Even Virchow's insistence on parenchymatous inflammation and inflammation of the single cell had to give way to the parenchymatous degenerations elaborated by Weigert, Zenker, Ziegler, and others. Chronic myocarditis presented a more difficult situation. Were the pale, hard areas of the indurated heart of early days—the connective or fibrous tissue areas of the later 19th century—signs of an inflammation starting in the heart muscle fibers, as Bouillaud, Kreysig, Hope, and Rokitsansky maintained? Or did they start as an inflammation in the interstitial tissue (Meckel, Corvisart)? Or were they not inflammatory at all, but manifestations of a sclerosis caused by complete or partial obliteration of the coronary branches—scars of an ischemic necrosis?

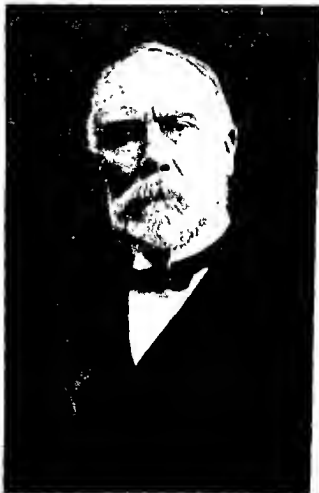


Figure I-22. Sir James Mackenzie (1853-1925). Portrait by Allan Barr. (Courtesy of Army Medical Library.)



Figure I-23 Robert Adams (1791-1875). Portrait at age 35. (Frontispiece of centenary number of *Irish Journal of Medical Sciences*, 1926. Reproduced in Kelly's *Medical Classics*, Williams & Wilkins)

Ziegler contributed his theory that myomalacia, the acute softening of necrosis, was caused by rapid thrombosis, and sclerosis by slow thrombosis. Weigert had a still better version of the pathogenesis of myocardial fibrosis when he added to the fibrosis following progressive obliteration of coronary branches, the general concept of replacement fibrosis in degenerated parenchymal tissue in general. Yet "chronic interstitial myocarditis" still remains the preferred term in a few pathologic, and more clinical, textbooks—a usage that is unjustified except perhaps in connection with rheumatic carditis, and rarely in syphilis. Thus, aided by Weigert's recognition of necrosis in 1880, we are led past the simple softening of Laennec, Quain's fatty degeneration and Ziegler's myomalacia, to the concept of myocardial infarction as a result of coronary insufficiency. The naming and establishment of this condition in the late 19th century as an important type of heart disease apparently cannot be attributed to any one individual.

The period and the rapidity of its rise in importance can be seen in our two great bibliographic lists (*The Quarterly Cumulative Index Medicus* and the *Index Catalogue of the Surgeon General's Library*), especially from 1916 on. The electrocardiograph can at present give with fair accuracy some idea of the existence and site of an infarct if in a favorable location, and some indication of its progress toward healing or scarring in the living individual.

The history of thyroid heart disease deserves some mention. "Enlargement of the thyroid gland in connection with enlargement or palpitation of the heart" had first been observed by Caleb Parry (1755-1822) in 1786 (Collection from his unpublished medical writings, 1825, 2:111-129). Hypothyroidism has been linked with cardiac changes only in the present century (H. Zondek, 1918; Blumgart, 1930). The pathogenetic and pathologic roles of the myxedematous thyroid in the accompanying cardiac condition still require further clarification. (See also pages 233, 525, and 582.)

Functional Disturbances of Heart Action. (See also Chapter V, B.) The story of the functional pathology of the heart, as already mentioned, extends over many centuries, but with a less concrete basis than that possessed by the structural kinds. It was not until the development of really useful instruments of precision (middle of 19th century) and the practical applications in ever increasing numbers of biophysical and biochemical methods (20th century) that knowledge of functional disturbances could with profit be objectively pursued. The extraordinary development of the latter methods has profoundly affected concepts of cardiac pathology like those of other systems of the body—the cause and pathogenesis of atherosclerosis, to take but a single example. Cardiac pain, dyspnea, edema, cyanosis, suggest very different and more complete pictures to the physician of today than they did to Heberden, John Cheyne, Stokes and Peacock. Today the flood of interrelationships of hormones, vitamins, enzymes and the like is so great that barriers of old classifications may well be destined to



Figure I-24. William Stokes (1804-1878). (From a drawing by Sir Frederick Burton.) (From *Major's Classic Descriptions of Diseases*, 2nd ed., courtesy of Charles C Thomas.)

disappear; and who, indeed, would venture to forecast what new alignments may result! However, in addition to being difficult to bring into established frames, this progress is all too recent and too rapidly changing to be properly treated historically.

Graphic instruments were especially important in developing knowledge of abnormal functioning of the heart and blood vessels: the sphygmomanometers of Vierordt (1854), Marey (1860), von Basch (1881, 1883), and others, leading to the Riva-Rocci type (1896), have long been universally used to estimate changes in blood pressure; Potain's (1867) and Mackenzie's (1902) polygraphs and Frank's capsule (1907), Waller's cardiac electrometer (1887), and Einthoven's (1903) string galvanometer have made it possible to register and explain hitherto unreachable changes in the heart action that are often of practical importance in exposing both abnormal action of the

several chambers and the electrical state of the heart muscle. In addition to the arrhythmias, which will be considered below and in Chapter V, B, are such functional disturbances as P. C. A. Potain's gallop rhythm (1885) and J. M. da Costa's "irritable heart" (1867); also the valvular murmurs, early heard through Laennec's stethoscope (1819), and Austin Flint's and Graham Steell's varieties which depend on complex disturbances in the intracardiac currents.

Cardiac Arrhythmias. Of the twenty-three varieties of cardiac irregularities covered in Chapter V, B, space permits historical consideration only of three of the more important: heart block, atrial flutter and atrial fibrillation. Heart block, the only group that has characteristic lesions, was first recognized as a clinical picture in the 18th century. The extremely slow pulse with apoplectiform seizures, and without residual paralysis, had been noted by Gerbezius (1719), Morgagni (1761), Th. Spens (1793), Wm. Burnett (1824) and doubtless also by others. Significant and more detailed accounts, however, were first given by Robert Adams (1827; Figure I-23) and the celebrated William Stokes (1846, Figure



Figure I-25. Wilhelm His, Jr. (1863-1931). (Reproduced with permission, from *Willis and Dry's A History of the Heart and Circulation*, W. B. Saunders Co.)

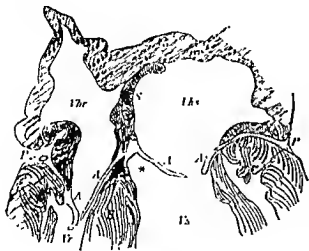


Figure I-26. Earliest illustration of the bundle of His (A-V bundle) to the left of small star. Drawing from heart of mouse, in His' original article in *Arbeiten der medizinischen Klinik zu Leipzig*, 1893. (In Library of College of Physicians of Philadelphia.)

I-24), so that the condition eventually became known as the Adams-Stokes syndrome. Many years had still to elapse, however, before its cause and nature were established. In addition to confirming Adams' case with reports of many other similar ones, Stokes made the shrewd observation of a remarkable pulsation in the right jugular vein, every third one very strong, the others much less, and some very minor. He could hardly have come closer to the concept of heart block without polygraphic aid and the anatomic knowledge furnished by the bundle of His and its lesions. This bundle was so briefly described by W. His, Jr. (Figure I-25) in 1893 (Figure I-26) as one item in a larger work, that it was forgotten until rediscovered in 1905. Similarly overlooked was his experimental demonstration (1895) that atrio-ventricular (A-V) dissociation was caused by damage to the bundle. In 1905 also, Joseph Erlanger produced complete block by experimental compression of the bundle; and even before the original discovery of the bundle, Gaskell (1883), Woolbridge (1883), and Tigerstedt (1884) had shown that compression of the atrioventricular groove would cause dissociation of the A-V rhythm. Also in 1905, A. Stengel reported a case of complete block caused by a sclerotic area extending from the mitral leaflet into the

bundle. In rapid succession, cases were found that were attributed to fibrosis (the commonest cause), syphilis, fatty degeneration of the muscle of the bundle, and fatty infiltration with compression, sclerosis, calcification and thrombosis of the nutrient artery. Very few carefully studied cases have been reported in which long-standing complete block was not found to be associated with an adequate lesion of the bundle of His.

Embryonal-like heart muscle fibers, similar to those comprising His' bundle, were shortly found in the sinoatrial node—the site of origin of the normal heart beat—by Keith (Figure I-27) and Flack in 1907, and at the base of the right atrium (the A-V node) by Aschoff and Tawara (1906). Disordered function of these two structures was soon found to be the cause of sinus arrhythmia and nodal rhythm, respectively. The demonstration (1906) by Tawara (born 1873) that the sub-endocardial Purkinje fibers linked His' bundle to the ventricular musculature established the existence of a special conductive system and promoted thereby a logical classification of the various arrhythmias.

Atrial flutter, a condition unknown till the



Figure I-27. Sir Arthur Keith (1866-1944). (Reproduced from Willis and Dry's *A History of the Heart and the Circulation*, by courtesy of W. B. Saunders Co.)

advent of instruments of precision, was first detected experimentally by A. P. Hertz and G. W. Goodheart (1909). Flutter was instrumentally recorded and named by W. A. Jolly and W. T. Ritchie in 1911.

Recognition of the nature of atrial fibrillation, one of the commonest of the serious types of arrhythmia, followed many years after its clinical manifestation, a lasting and grossly irregular pulse, had become known and studied. James Mackenzie, whose life-long study of the heart and its arrhythmias opened new paths in the concept of heart disease, tells in his *Diseases of the Heart* (third edition, 1913) a fascinating story of how the correct knowledge of one condition was reached: "My attention was first directed to

this condition as a separate and definite entity about 1890." The *pulsus irregularis perpetuus*, so named by Hering in 1903, was shown by Mackenzie's polygraph (recording jugular, radial and apex waves) always to lack the auricular (atrial) wave in the jugular record. His first thought that this was due to nodal rhythm was negated by A. R. Cushny and C. W. Edmonds getting similar radial tracings from a dog in which visible fibrillation had been produced experimentally (1906). This was confirmed in 1909 by Rothberger and Winterberg, using the newly discovered electrocardiograph, and by Thomas Lewis both experimentally and clinically with the same instrument (1909, 1910).

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The Development of the Heart

BRADLEY M. PATTEN

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THE PLAN OF THE EMBRYONIC CIRCULATION AND ITS FUNCTIONAL SIGNIFICANCE

ANY ACCOUNT of the prenatal development of the heart which is limited to an entirely morphologic approach inevitably will be disappointing as a basis for understanding cardiac physiology or pathology. The embryonic heart can be intelligently studied only in relation to its changing functional rôle as the plan of the embryonic circulatory system is altered during development. It is unnecessary to be concerned, in most instances, with peripheral vessels, but the changes in the main blood streams that enter and leave the heart must be borne clearly in mind in order to understand the structural changes occurring in the heart itself. If one uses as a basis of approach certain fundamental conceptions as to the significance of the circulatory system in organic economics, and the evolutionary principle that any embryo must go through certain ancestral phases of organization before it can arrive at its adult structure, then the

changes in arrangement of vascular channels and the different routings of blood through the heart during the course of development will form a coherent and logical story.

In the embryo, as in the adult, the main vascular channels lead to and form the centers of metabolic activity. The circulating blood carries food from the organs concerned with its absorption to parts of the body remote from the source of supplies; oxygen to all the tissues of the body from organs that are especially adapted to facilitate the taking of oxygen into the blood; and waste materials from the places of their liberation to the organs through which they are eliminated. One of the primary reasons the arrangement of the vessels in an embryo of a mammal differs so much from that in an adult is that the embryo lives under conditions totally unlike those which surround its parents. Its centers of metabolic activity are, therefore, different;

and, since the course of its main blood vessels is determined by these centers, the vascular plan is different.

The organs which in the adult mammal carry out such functions as digestion and absorption, respiration, and excretion are extremely complex and highly differentiated structures. They are for this reason slow to attain their definitive condition and are not ready to become functional until toward the close of the embryonic period. Moreover, conditions surrounding certain of the developing organs during intra-uterine life absolutely prevent them from becoming functional even were they sufficiently developed to do so. Suppose the lungs, for example, were functionally competent at an early stage of development. Inasmuch as the embryo is reliving ancestral conditions in its private amniotic aquarium, its lungs are as incapable of functioning as those of a man under water. Likewise, the developing digestive organs of the embryo are inaccessible to raw food materials. Further examples are not necessary to make it obvious that, were the embryo dependent on the same organs that carry on metabolism in the adult, development would be at an impasse.

An embryo must, nevertheless, solve the problem of existence during the protracted time in which it is building up a set of organs similar to those of its parents. In the absence of a dowry of stored food in the form of yolk, the mammalian embryo draws upon the uterine circulation of the mother. Utilization of this source of supplies depends on the development of a special organ which serves through fetal life and is then discarded. The embryo takes food not into its slowly developing gastrointestinal tract but into its chorion, a membrane projected outside its own body and applied to the inner lining of the uterus to form the placenta. The nutritive materials there absorbed from the maternal blood must be transported to the growing embryo by its own blood stream.

The use of food materials to produce the energy expressed in growth depends on the presence of oxygen. For growth, there must be a means of securing oxygen and carrying

it, as well as food, to all parts of the body. Nor can continued growth go on unless the waste products liberated by the developing tissues are eliminated. The blood of the embryo cannot be relieved of its carbon dioxide and acquire a fresh supply of oxygen in the primordial cell clusters that will later become its lungs. It cannot excrete its nitrogenous waste products through undeveloped kidneys. Its respiration and excretion, like its absorption of food, are carried out in the rich plexus of small blood vessels in the chorion. Here the fetal blood is separated from the maternal by tissues so thin that it can readily give up its waste materials to, and receive food and oxygen from, the maternal blood stream, just as the mother's own tissues constantly carry on this interchange with the circulating blood. The placenta is thus the temporary alimentary system, lungs, and kidneys of the mammalian embryo. The enormous chorionic blood supply during fetal life, and the entire disappearance of this special arc of the circulation when the organism assumes adult methods of living, is a very striking example of the determination of vascular channels by the location of functional centers. We must not, however, overlook the fact that there are many other centers of activity in the growing embryo less conspicuous but equally important for its continued existence. Each developing organ in the embryonic body is a center of intense metabolic activity. During fetal life it must be supplied by vascular channels adequate to care for its growth.

But that is not all. Up to the time of birth each organ has been drawing on blood furnished with food and freed of waste materials by the activities of the maternal organism. At birth all this must change. Each organ essential to metabolism must be ready to assume its own active share in the process. Their vessels must be adequate to provide, not only for the needs of these organs, but also for the new functions these organs assume in maintaining the metabolism of the organism as a whole.

While the functional significance of the arrangement of the blood vessels is of primary importance, especially in understanding the progressive changes in vascular plan, there

is another factor which we cannot overlook. This factor is conservative, having to do with the things we inherit from our forebears. The goal of the embryonic period is the attainment of a bodily structure similar to that of the parents. Because it is so familiar, we accept with complaisance the remarkable fact that this goal is attained with absolute regularity. There may be accidents leading to defective development or malformation, but the fertilized ovum of one species always gives rise to an individual of that species and to no other. The new individual will show detailed differences from its parents, differences which are capitalized in the slow march of evolution; but in a single generation these differences are never radical. We say that the offspring has inherited the structure of its parents. It does more; it inherits the tendency to arrive at its adult condition by passing through the same sort of changes which its ancestors underwent in the countless millions of years it took their present structure to evolve.

Applied to the development of the circulatory system of the human embryo, this means that the earliest form in which it appears will not be a miniature of the adult circulation. The simple tubular heart, pumping blood out over aortic arches to be distributed over the body and returned to the posterior part of the heart by a bilaterally symmetrical venous system—in short the vascular plan which we see in young mammalian embryos (Figure II-15)—is essentially the plan of the circulation in fishes. When we realize this, we are not puzzled by either the appearance of a full complement of aortic arches or their subsequent disappearance to make way for a new respiratory circulation in the lungs. We see

the march of progress from a logical beginning in ancestral conditions toward the consummation of fetal life with an organization like that of the parent.

In addition to the fundamental ground plan of the circulation of the mammalian embryo, recapitulations account for many transitory peculiarities. The formation of a conspicuous, though empty, yolk-sac with a complement of blood vessels almost as well developed as the vitelline vessels of animals well endowed with yolk is clearly a recapitulation of ancestral conditions. So, also, is the highly developed system of venous channels in the mesocephalos. If the organ itself appears, it brings with it its quota of vessels, no matter if the organ is destined to degenerate later in development.

Whatever peculiarities may be impressed on the course of the circulation by the appearance of ancestral structures, or by the development of special fetal organs such as the yolk-sac and the placenta, the main blood currents will at any time be found concentrated at the centers of activity. Changes of these main currents as one center retrogresses and another becomes dominant must take place gradually. Large vessels become smaller, what was formerly an irregular series of small vessels becomes excavated to form a new main channel, but the circulation of blood to all parts of the body never ceases. Even slight curtailment of the normal blood supply to any region would stop its growth; any marked local decrease in the circulation would result in local atrophy or malformation; complete interruption of any important circulatory channel, even for a short time, would inevitably mean the death of the embryo.

THE ESTABLISHING OF THE PRIMARY EMBRYONIC CIRCULATION

The human embryo, having practically no yolk available as food, is dependent for its survival and growth on the prompt establishment of relations with the circulation of the mother. This implies the necessity of a precocious development of the vascular system

of the embryo, for the maternal circulation remains confined within the uterine walls and the embryonic circulation must grow to it. Until this is accomplished, the embryo is dependent on what food material it can obtain from the uterus by direct absorption—a

method entirely inadequate to provide for its growth except in very early stages when the bulk of the embryo is inconsiderable.

The Cardiopericardial Primordium. The primordial tissue aggregation which is the precursor of both the heart itself and the lining of the primitive pericardial region of the coelom is a crescentic zone of thickened mesoderm (Davis, 1927). This zone first becomes clearly defined in human embryos in the primitive-streak stage (fertilization age about 15 days). It is located in front of the embryonic disk and swings around to either side, following the curvature of the cephalic margin of the disk (Figure II-1A). When this thickened mesodermal area first becomes recognizable it is not yet split into splanchnic and somatic layers (Figure II-2A). Even in this very early stage, in forms such as the chick which lend themselves to experimental procedures, it is possible to demonstrate the cardiogenic potentialities of cells within this area by explanting them and allowing them to differentiate as grafts on the chorio-allantois of older chicks. Under such circumstances the cells in question will develop myofibrils and clearly declare their myocardial potencies by their rhythmic pulsation.

A day or two later than the primitive-streak stage, the thickened zone of mesoderm becomes split into somatic and splanchnic layers, thereby establishing vesicular spaces which soon coalesce to make a cavity that is destined to be the pericardial part of the coelom (Figures II-1B and II-2B). Concurrently, the head of the embryo has been growing rapidly and has pushed out over the newly formed pericardial coelom (Figure II-2B, C). At the same time the pericardial part of the coelom is extended by further splitting of the mesoderm, so that it sweeps back on either side of the body, following the curve of the foregut (Figure II-1C).

The Formation of the Heart. Once the pericardial cavity is thus established, one can drop the cumbersome term "cardiopericardial primordium" and speak of the *cardiac primordia* which take shape at specific locations within this general area. The cardiac primordia are formed from the splanchnic mesodermal layer of the primitive pericardial cavity, on either side, where it lies close against the developing foregut (Figures II-1C and 3A). The fact that the heart, a median unpaired structure in the adult, arises from paired primordia which at first lie widely separated

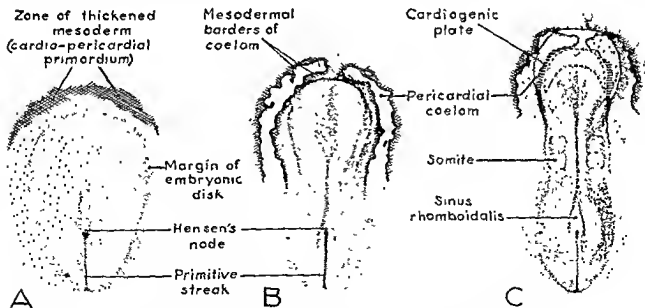


Figure II-1. Diagrams showing the location of the cardiopericardial primordia in embryos early in the third week of development. The cross-hatched area in A represents the zone of thickened mesoderm before the formation of coelomic cavities. The light areas in B and C represent the coelomic cavities as if they were seen through a semitransparent embryonic body. The broken lines in C show the position of the foregut. (Based in part on the work of Davis, *Carnegie Contrib. to Embryol.*, Vol. 19, 1927.)

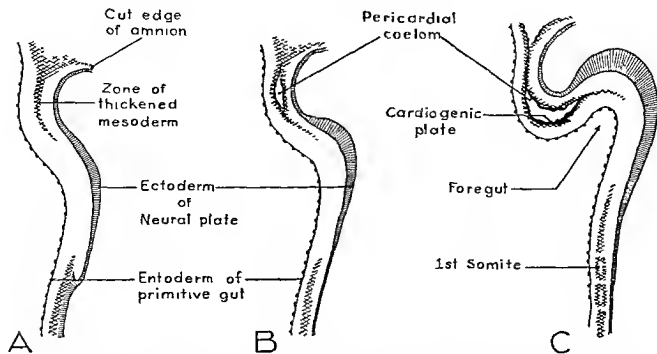


Figure II-2. Longitudinal sections of embryos early in the third week of development showing the way the cardiopercardial primordium, which at first lies in front of the cephalic margin of the embryonic disk, is overridden by the forward growth of the head. As the foregut is formed within the head, the cardiopercardial primordium is turned under it and extends back on either side, flanking the anterior intestinal portal. (Based in part on the work of Davis, *Carnegie Contrib. to Embryol.*, Vol. 19, 1927.)

on either side of the midline is correlated with the fact that the embryonic body at first is open ventrally and lies spread out prone on the surface of the yolk-sac. The primordia of certain anatomically ventral structures arising at an early stage of development, therefore, first appear as separate halves lying on either side of the midline. With the folding under of the lateral margins of the embryonic area, which brings the ventrolateral walls of the body into their definitive position, the embryo is closed ventrally, and potentially midventral structures which arose as separate halves are established in the midline.

The primordial heart is double-layered, as well as paired right and left. The inner layer is called the *endocardium* because it is destined to form the internal lining of the heart. The outer layer is known as the *epimyocardium* because it will give rise to both the muscular layer of the heart wall and its epicardial investment.

The endocardium, when it first appears, is in the form of irregular clusters and cords of mesenchymal cells lying between the splanchnic mesoderm and the entoderm (Figure

II-3A). These cells become organized into two main strands, lying one on either side of the gut. Soon after their establishment, the strands acquire a lumen and are known as the *endocardial tubes* (Figure II-3B). The endocardial tubes continue beyond the cardiac region as branching strands which will become, cephalically, the primitive ventral aortic roots and, caudally, the veins entering the heart (Figure II-4A). The splanchnic mesoderm soon becomes markedly thickened where it is reflected laterally over the endocardial tubes to constitute the epimyocardial layer of the heart (Figure II-3B).

Meanwhile, folding-off of the embryonic body continues with concomitant progress in the closure of the foregut at the level of the heart. As a result, the paired endocardial tubes are brought progressively closer together. Finally, they are approximated to each other and fuse to form a single tube lying in the midline (Figures II-3C, D and II-4B). In the same process, the *epimyocardial layers* are bent mesially, completely enveloping the endocardium. Ventral to the heart, the *mesodermal layers* of the opposite sides

of the body become continuous with each other so that, in the same process which establishes the heart as a median structure, the originally-paired right and left coelomic chambers become confluent to form a median pericardial cavity (Figure II-3C, D). Dorsally, the right and left epimyocardial layers become contiguous, but here they do not fuse immediately, as happens ventral to the heart. They persist for a time as a double-layered supporting membrane, called the *dorsal mesocardium*. In this manner, the heart is established as a nearly straight, double-walled tube suspended mesially in the most anterior part of the coelom.

Cardiac Jelly. Even at this early stage, interesting histogenetic changes are beginning to become apparent. The endothelial nature of the endocardial primordia is clearly evident in the configuration of their constituent cells, and in the littoral relation of the cells to the

developing lumen of the heart. This inner endothelial layer of the cardiac tube is held in relation to the outer, epimyocardial layer by a gelatinous substance called "*cardiac jelly*" (Davis, 1927). The cardiac jelly is so translucent and structureless that it is easily overlooked unless one observes the mechanical evidences of its presence in living material. If a beating embryonic heart in the tubular stage is transected, one sees the endothelial layer follow every movement of the pulsating epimyocardial sleeve which encloses it (Patten, Kramer and Barry, 1948). In the absence of any internal fluid pressure, this can be accounted for only on the basis of the supporting and cohesive action of the cardiac jelly between these two layers (Barry, 1948).

In its fixed condition cardiac jelly appears as a delicate meshwork of coagulated material, at first entirely devoid of cells (Figure II-5a). As development progresses, cells appar-

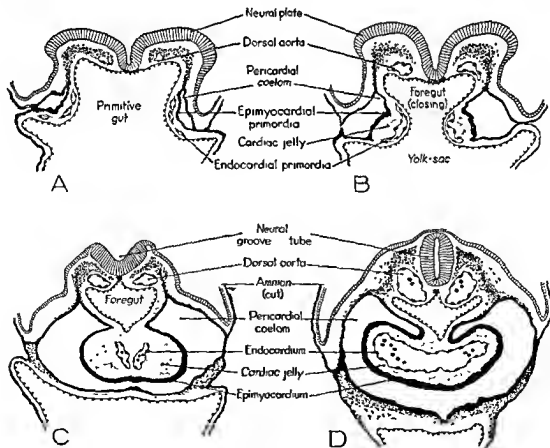


Figure II-3. Four stages in fusion of paired primordia of heart as seen in cross section of young human embryos. A. Based on the Ludwig, two-somite embryo. B. Based on the Carnegie 3709, four-somite embryo. C. Based on the Payne, seven-somite embryo. D. Based on the Corner, 10-somite embryo. (From Patten, *Human Embryology*, courtesy of The Blakiston Company.)

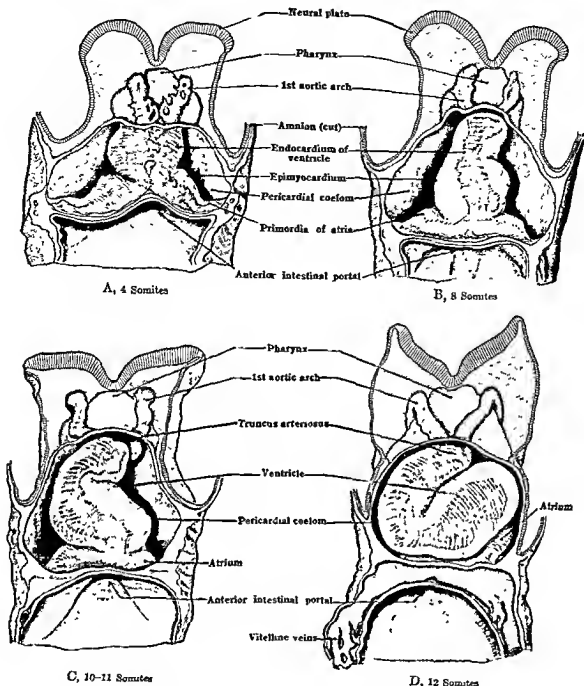


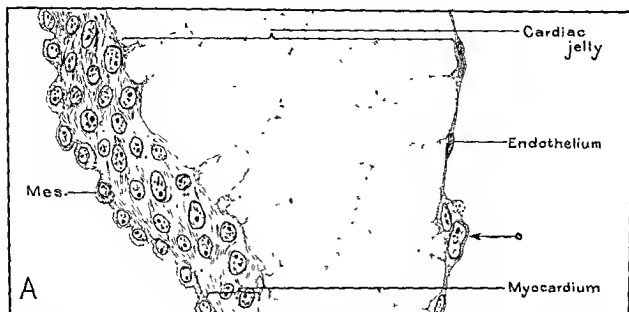
Figure II-4. Four stages in formation of heart exposed by ventral dissection (Based on the figures of Davis, *Carnegie Contrib to Embryol.*, Vol. 19, 1927. From Patten, *Human Embryology*, courtesy of The Blakiston Company.)

Figure II-5. Drawings showing stages in the cellular invasion of cardiac jelly with the resultant formation of endocardial cushion tissue. All the drawings were made from comparable areas in the conotruncus to the same scale (original X 1000, reproduced X 750). (From Patten, Kramer and Barry, *Anat. Rec.*, Vol. 102, 1948.)

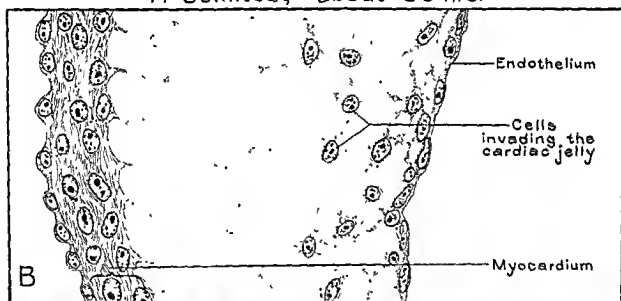
A. From a 14-somite chick (± 36 hours), showing the primary noncellular character of the cardiac jelly. Note the thinness of endothelium except for the place indicated by the arrow.

B. From a 33-somite chick (± 65 hours), showing the beginning of cellular invasion. Note the thickened character of the endothelium and that cells have not as yet reached the myocardium.

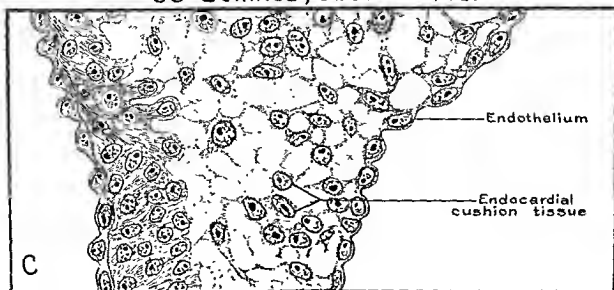
C. From a 40- to 41-somite chick (± 84 hours), showing cells throughout the territory formerly occupied by the cardiac jelly alone.



14 Somites, about 36 hrs.



33 Somites, about 65 hrs.



40-41 Somites, about 84 hrs.

ently arising from the endothelium invade the cardiac jelly and become organized into the primitive plastic type of connective tissue which is commonly called *endocardial cushion tissue* (Figure II-5B and C). Local masses and ridges of this endocardial cushion tissue we shall see playing an important rôle in the partitioning of the heart and in the molding of its valves. In the areas not so specialized, thin layers of this same tissue form the sub-endothelial connective tissue stratum of the adult endocardium.

Histogenesis of Cardiac Muscle. The mesothelial character of the cells which constitute the layer of the epimyocardium adjacent to the pericardial cavity is, from the first, quite evident (Figures II-5 and II-6A). The inner part of the epimyocardium gives rise to the muscular tissue of the cardiac wall. In the early stages of their differentiation, the cells of the myocardium are packed closely together, with little indication of any definite plan of arrangement. About the time the first contractile activity begins, the nuclei are somewhat less close together and, with the light microscope, no trace of cell boundaries can be seen in the cytoplasm. It is at about this time, also, that a suggestion of the formation of myofibrils begins to be recognizable.

Not long after their first appearance, the young myofibrils become conspicuous. They are much larger than the fibrils of more mature cardiac muscle and show definite dark bands, owing to local concentration of anisotropic substance (Figure II-6B). At this early stage the myofibrils are relatively few in number and pursue a startlingly irregular course, frequently crossing one another. They traverse the cytoplasm for considerable distances, apparently not being restricted to any limited cytoplasmic areas such as might have been derived from single cells before their boundaries became indistinguishable.

The later stages in the histogenesis of cardiac muscle are along the lines one would expect from a knowledge of its adult structure. As the growing muscle is pulled into spiral bands about the developing chambers of the heart, the strands of myocardium gradually become less irregular in their arrange-

ment. In sectioned material from the hearts of embryos of the third month, areas appear showing groups of fibers running more or less parallel to each other and crossing other groups of fibers at varying angles. The myofibrils have become more abundant, and lining up of the dark and light portions of adjacent fibrils is beginning to give the muscle a cross-striated appearance (Figure II-6C). In comparing fetal with adult cardiac muscle, the further increase in the number of myofibrils and their decrease in coarseness are most striking (cf. C and D in Figure II-6).

The last of the characteristic histologic features of cardiac muscle to make their appearance are the intercalated disks. These curious transverse markings seem to appear at sites where one could readily believe adjacent cellular elements originally made contact. Indeed, electron microscope studies show that the adult disks are really cell membranes with secondary specializations. This may mean that the disks appear at the site of cell boundaries not seen with the light microscope.

Primary Regional Divisions of Heart. Returning from the consideration of histogenetic changes to the general configuration of the growing heart, we find that very early in development the dorsal mesocardium disappears except for a persistent portion at its caudal end (cf. Figures II-30A and B). Thus the tubular heart comes to lie in the pericardial cavity, attached only cephalically where the ventral aortic roots branch out into the tissue beneath the foregut, and caudally where the great veins enter (Figure II-7). Being unattached in its midportion, it is free to change its shape and position and, since it grows much more rapidly in length than does the pericardial part of the coelom in which it is situated, the originally straight heart tube soon becomes conspicuously bent (Figures II-4C, D and II-7).

With the elongation and bending of the cardiac tube, its primary regional divisions begin to be recognizable. Naming them in the order they are traversed by the circulating blood, these regions are the sinus venosus, the atrium, the ventricle, and the truncus arteriosus (Figure II-8). The *sinus venosus* is

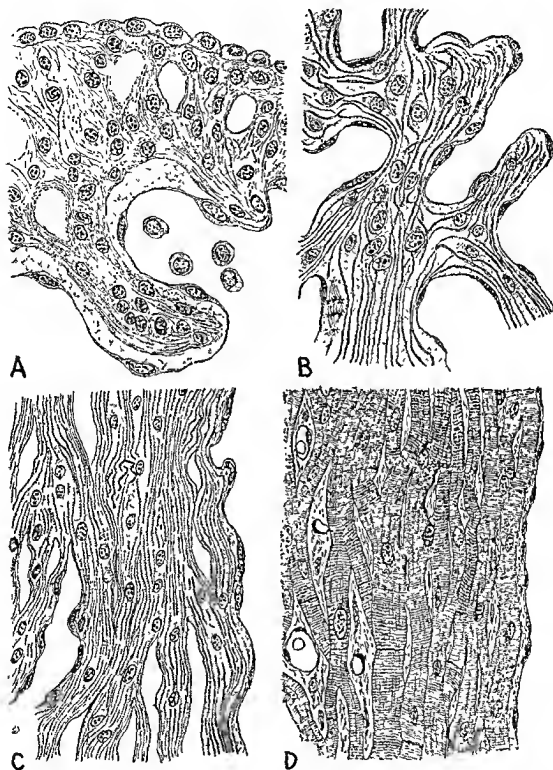


Figure II-6. Histogenesis of cardiac muscle. (Camera lucida drawings, X 500.) A. Entire thickness of ventricular wall of 45-mm. embryo. B. Developing trabeculae from inner part of ventricular wall of 9-mm. embryo. C. Inner part of ventricular wall of 45-mm. embryo. D. Inner part of adult right ventricular wall. (From Patten, *Human Embryology*, courtesy of The Blakiston Company.)

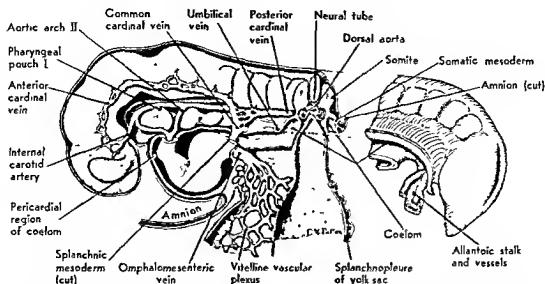


Figure II-7. Schematized lateral dissection of human embryo of about three weeks, to show continuity of pericardial portion of coelom with paired coelomic chambers of midbody region. (Based, in part, on Heuser's study of a 14-somite embryo, *Carnegie Coll.*, 4529. From Patten, *Human Embryology*, courtesy of The Blakiston Company.)

a thin-walled chamber formed by the confluence of the great veins entering the heart (Figure II-30C). Since the fusion of the cardiac primordia begins at their cephalic ends and progresses caudad, the sinus venosus is the last part of the heart to be established and at early stages shows but slight differentiation.

From the sinus venosus the blood passes into the atrium. Guarding the slit-like orifice between these two chambers against the return flow of blood are well-developed flaps known as the *valvulae venosae* (Figures II-16 and II-18). The atrial region, soon after it is established, undergoes extensive transverse enlargement so that it bulges out into pouch-like right and left chambers (Figure II-8). Although the beginning of the separation of these chambers from each other is clearly indicated as early as the fifth week by the presence of an interatrial septum, this septum is not immediately completed and the atrial chambers remain for a time in communication caudally by an opening called the *primary interatrial foramen* or, more briefly, *ostium I* (Figures II-16 and II-29B, C).

Leaving the atrium, the blood passes to the ventricle through a constricted region known as the *atrioventricular canal*. The ventricle is formed from the most sharply bent part of the cardiac tube (Figure II-4C and D). Correlated with its activity in pumping,

the ventricular wall becomes greatly thickened, with irregular branching bands of developing muscle tissue protruding from the main part of the wall into the lumen (Figure II-6A). These primordial trabeculae carneae already suggest the muscular bands which project so characteristically into the cavities of the adult ventricles. From the ventricle the blood passes into the *truncus arteriosus* and thence out to the body by way of the ventral aortic roots.

It should not be inferred from the modifications which have occurred in the different regions of the heart that it has as yet altered its primitive method of functioning. The heart tube becomes bent and shows local dilations and constrictions which we are able to name because we know their future fate. Many internal conditions point toward its division into right and left sides. But the blood in the early stages of development enters the heart dorsally by way of the sinus venosus, is collected in the atrium, and passes into the ventricle whence it is pumped out by way of the *truncus arteriosus* as an undivided stream.

The Primary Arterial Channels. While these changes have been occurring in the cardiac region, the main vascular channels characteristic of young embryos are making their appearance (Bremer, 1914). The cephalic prolongations of the endocardial tubes beyond the

cardiac region constitute the start of the main efferent channels or aortae. The aortae are further extended by a process similar to that involved in the formation of the endocardial tubes themselves. Cords and knots of cells of mesodermal origin become aggregated along the course of the developing vessel. These strands of cells are then hollowed out to form tubes, walled by a single layer of endothelial cells. Where main blood vessels are about to become established, there is found first a meshwork of these small channels (Evans, 1909). Gradually some of these primitive channels are enlarged and straightened to form the main vessels, and their walls are later reinforced by the addition of circularly disposed connective-tissue fibers and smooth muscle cells. In this manner, the primitive efferent channels are prolonged from the heart cephalad, beneath the pharynx, as the *ventral aortae*. They then bend laterally and dorsally about the pharyngeal walls to form aortic

arches, and finally turn caudad to extend nearly the entire length of the embryo as the *dorsal aortae* (Figure II-15).

At first, there is but a single pair of *aortic arches* which is located in the tissue of the mandibular arch (Figure II-9A). Later in their development, vertebrate embryos in general tend to form five additional pairs of arches connecting the ventral and dorsal aortae (Figure II-10A). Each of these aortic arches lies in one of the visceral arches caudal to the mandibular. The entire series of aortic arches, however, is never present at the same time in mammalian embryos, for the first two arches degenerate before all of the more caudal ones are formed, and the fifth is rudimentary and often wanting altogether (Congdon, 1922). From the functional standpoint, the significant thing is that blood passes by way of one or more pairs of aortic arches around the pharynx from the ventrally located heart to the dorsally located aortae which are the main

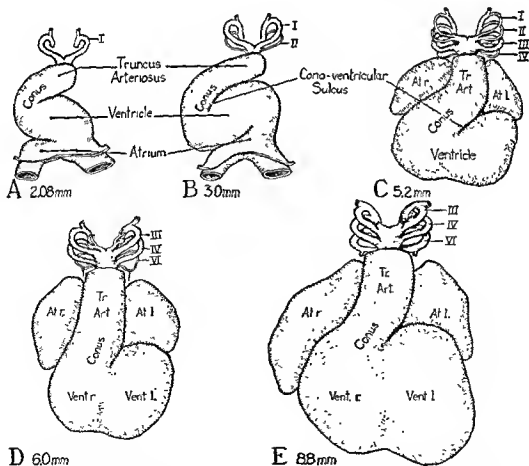


Figure II-8. Ventral views of human embryonic hearts, to show bending of cardiac tube and establishing of regional divisions. (After Kramer, *Am. J. Anat.*, Vol. 71, 1912.)

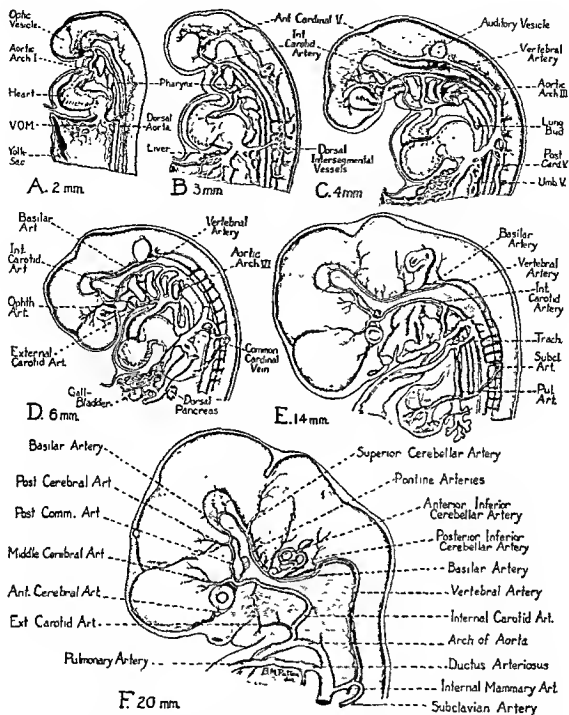


Figure II-9. Development of aortic arches and cerebral vessels in human embryos. (Based, in part, on the work of Congdon, *Carnegie Contrib. to Embryol.*, Vol. 14, 1922, from Patten, *Human Embryology*, courtesy of The Blakiston Company.)

distributing trunks of the embryonic circulation. In human embryos of one month, the first three aortic arches are well formed and the fourth is usually just making its appearance (Figure II-15). By the time the embryo has reached a size of 10-12 mm., that is to say six weeks after fertilization, the first and

second arches have degenerated and the aortic arches present are the third, fourth, and sixth of the series (Figures II-9 and II-10).

Throughout the length of the aorta, small branches appear at regular intervals and extend dorsad on either side of the neural tube.

Since these vessels are formed between adjacent somites, they are known as the *dorsal intersegmental arteries* (Figure II-15). Most of the important branches of the aorta arise either from these dorsal intersegmental vessels or from another series of segmentally arranged branches which extend ventrally, and

still others which extend laterally in the growing body (Figure II-11).

When first formed, the dorsal aorta is, as we have seen, a paired vessel (Figure II-11A). This paired condition is retained in the branchial region, but caudally the two primitive aortae soon fuse to form a median vessel

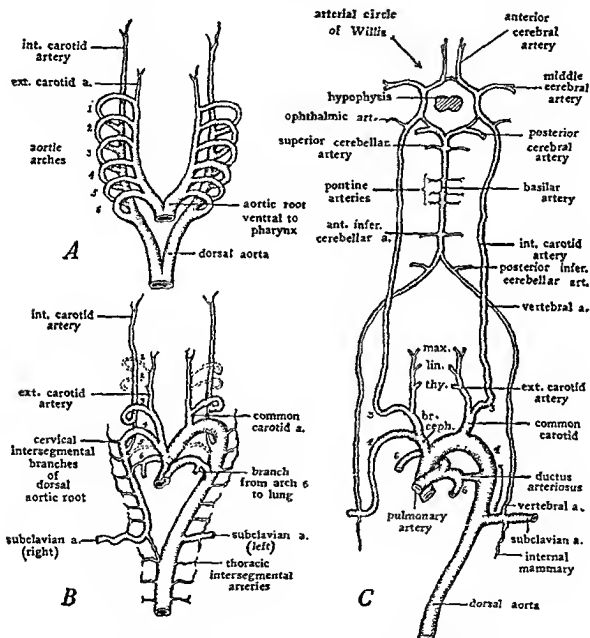


Figure II-10. Diagrams illustrating changes which occur in aortic arches of mammalian embryos. (From Patten, *Human Embryology*, courtesy of The Blakiston Company.) A. Ground plan of complete set of aortic arches. B. Early stage in modification of arches. C. Adult derivatives of aortic arches.

Abbreviations: br. ceph., brachiocephalic (Innominate) artery; lin., lingual artery; max., maxillary artery; thy., thyroid arteries. Figure II-9 shows from another view, and less schematically, some of the changes summarized in this illustration.

The arrow in the lower part of C indicates the change in position of origin of left subclavian artery which occurs in the later stages of development

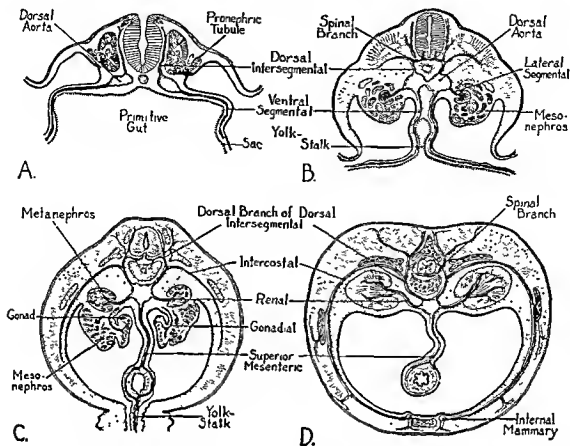


Figure 11-11. Cross-sectional plans of the body showing relations of segmental branches of aorta at different stages of development. (From Patten, *Human Embryology*, courtesy of The Blakiston Company.)

(Figure 11-11B, C). The fusion first occurs in the midbody region and extends thence cephalad to about the level of the anterior appendage buds and caudad throughout the length of the aorta.

In young embryos, the most conspicuous vessels arising ventrally from the dorsal aorta are the *allantoic or umbilical arteries*, which supply the vascular plexus of the chorion, and the *omphalomesenteric arteries* which are prolonged as the vitelline arteries to the yolk-sac (Figure 11-15). These vessels arise from the aortae before their fusion and, being derived by enlargement of its primitive ventral segmental branches at the levels concerned, are at first paired, right and left (Ingalls, 1920). The umbilical arteries retain their paired condition but, when the body is closed ventrally, the right and left omphalomesenteric roots are brought together in the mid-line and fuse to form a median vessel running in the mesentery (Figure 11-11). With the

early degeneration of the yolk-sac, this vessel becomes relatively less conspicuous and is known as the *superior mesenteric artery* (Figure 11-11C, D). Its original relations are, nevertheless, apparent from its course along the intestinal loop into the belly-stalk to the place where the small yolk-sac still retains its attachment to the gut.

The Primary Venous Channels. The main vessels first serving to collect the blood which is distributed to all parts of the embryo by branches from the aortae are the cardinal veins. They arise by an entirely similar process but become clearly defined somewhat later than the aortae. There are at first two pairs of these vessels, the *anterior cardinal veins* draining the cephalic, and the *posterior cardinal veins* draining the caudal region of the body. At the level of the heart the anterior and posterior cardinal veins on either side of the body become confluent as the *common cardinal veins*, or *ducts of Cuvier*. The common

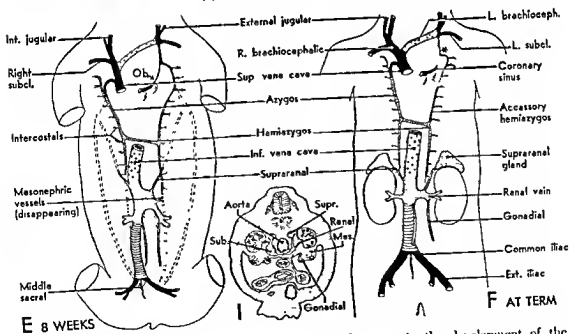
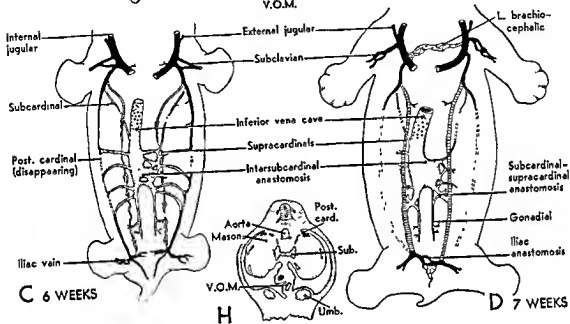
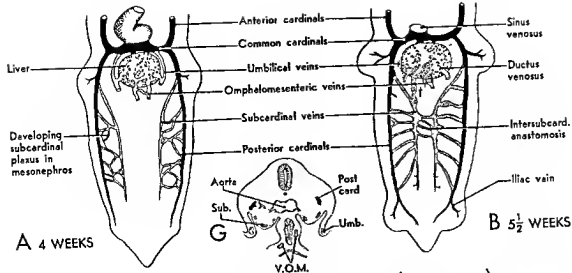


Figure 11-12. Schematic diagrams showing some of the steps in the development of the inferior vena cava. (From Patten, *Foundations of Embryology*, courtesy of the McGraw-Hill Book Company. Based on the work of McClure and Butler.) Cardinal veins are shown in black, subcardinals are stippled, supracardinals are horizontally hatched. Vessels arising independently of these three systems are indicated by small crosses. Abbr.: Ob., oblique vein of left atrium, *, left superior intercostal, †, mesenteric portion of inferior vena cava.

cardinals are short trunks which at once turn ventromesial and enter the dorsocaudal part of the heart (Figures II-12A and II-15).

Little alteration from primitive conditions occurs, at early stages, in the veins of the ventral part of the body. Numerous large tributary vessels appear, especially in the cephalic region where they converge on either side of the head as the so-called *veuae capitis*. It is already possible to recognize in the larger of these branches the primordial vessels from which the main venous sinuses of the adult cranial region are derived. Fundamentally, nevertheless, these veins are but an elaboration of the original anterior cardinal system.

In very young embryos, the posterior cardinal veins are the only conspicuous venous channels draining the caudal half of the body (Figures II-12A and II-15). By six weeks, however, new vessels have appeared and, while the relative position of the posterior cardinals as vessels lying dorsal to the mesonephroi remains unchanged, much of the blood formerly returned by them now reaches the heart by way of new channels. As a result, the posterior cardinal veins in the midmesonephric region begin to undergo regressive changes. The new vessels which thus bring about the diversion of the blood from the posterior cardinals are the *subcardinal veins* (Figure II-12). When they first appear, these vessels are but an irregular plexus, tributary to the posterior cardinals (Figure II-12A). The organization of longitudinal channels in these plexuses establishes the main subcardinal veins as vessels extending cephalad in the ventromesial border of the mesonephroi, parallel with, and ventral to, the posterior cardinal veins. In the cephalic part of the mesonephros, the newly established subcardinal blood stream enlarges some of the small channels already entering the posterior cardinal and discharges through them into the posterior cardinal vein (Figure II-12B).

With the growth of the mesonephroi the rapidly enlarging subcardinal veins are brought very close to each other. Where they are approximated, cross-communication is established, first by small vessels (Figure II-

12B) and then by a broad *intersubcardinal anastomosis* (Figure II-12C, D). The large median *subcardinal venous sinus* thus formed probably offers less resistance to the flow of blood than surrounding channels; in any case, all the vessels connecting with it tend to drain toward it (Butler, 1927).

One might expect that the great volume of blood entering the subcardinal sinus would cause a corresponding enlargement of the cephalic portion of one or both subcardinal veins. Instead, a new and more direct channel toward the heart appears. In its growth, the liver is crowded very close to the mesonephroi. The developing liver contains a maze of vascular channels, as does the mesonephros. Capillaries ramifying in the base of the mesentery between the liver and the mesonephros form the connecting link between the two organs. Once the blood begins to find its way by this route, the small irregular channels are rapidly enlarged and straightened to form the primordium of the *mesenteric portion of the inferior vena cava* (McClure and Butler, 1925; McClure and Huntington, 1929; Reagan, 1929). The new and more direct channel thus established leads from the subcardinal sinus through the right subcardinal vein for a short distance, and thence by the newly excavated channels in the mesentery, through the liver, to the heart (Figure II-12B).

The venous return of blood from the yolk-sac circulation, and later from the developing placental circulation also, reaches the heart by way of the liver. At first the *omphalomesenteric veins* pass along either side of the yolk-stalk and the developing walls of the gut-tract to enter the *sinus venosus* directly (Figure II-13A). The growing liver, however, soon encroaches on their proximal portions so that, instead of being returned to the heart by the original main veins, the blood is routed through a maze of small channels ramifying among the developing cell cords of the liver (Figures II-9B-D and 13B, C). Leaving the liver, the blood of this circuit is re-collected to join the stream coming back from the body by way of the developing inferior vena cava (Figure II-13C, D).

The *umbilical veins* which return the blood

from the chorion to the heart are, at first, paired vessels traversing the belly-stalk and the lateral body-walls of the embryo (Figure II-15). Their original direct course through the body-walls to the sinus venosus does not, however, long persist. As was the case with the vitelline circulation, the growing liver interrupts the umbilical veins. The underlying

factor in this process is the extensive growth of the liver which brings it into contact with the lateral body-walls in which the umbilical veins are embedded. Fusion follows the contact and small vessels develop between the umbilicals and the network of channels in the liver (Figure II-13B). As these new vessels develop, the portions of the umbilical

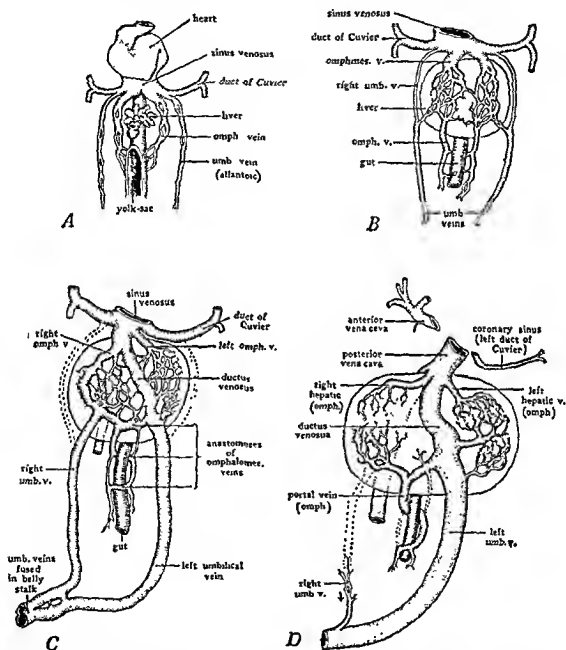


Figure II-13. Diagrams showing development of hepatic portal circulation from omphalomesenteric veins, and changes by which blood returning from placenta by way of umbilical veins is rerouted through the liver. (From Patten, *Human Embryology*, courtesy of The Blakiston Company.) A. Based on conditions in pig embryos of 3-4 mm., applicable to human embryos of fourth week. B. Based on pig embryos of about 6 mm., applicable to human embryos of fifth week. C. Based on pig embryos of 8-9 mm., applicable to human embryos early in sixth week. D. Based on pig embryos of 20 mm. and above, applicable to human embryos of seven weeks and older.

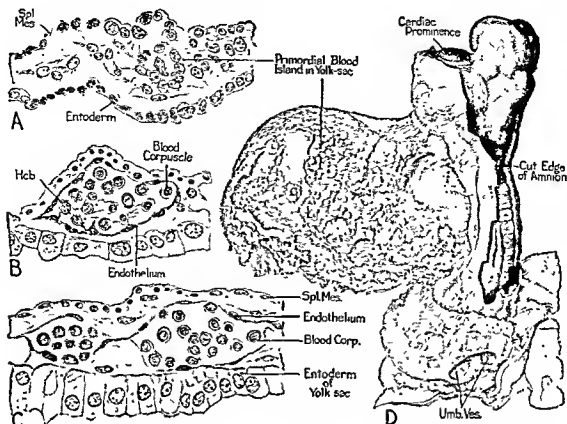


Figure II-14 Development of yolk-sac blood islands. A C are camera lucida drawings, reproduced X355. A. Early stage in aggregation of cells between entoderm and splanchnic mesoderm in yolk-sac of an embryo early in fourth week (17 somites). B. Beginning of differentiation of endothelium and primitive blood cells, from an embryo of about four weeks (4.5 mm). C. A more advanced area from a four-week embryo showing endothelium well differentiated and corpuscles suspended free in plasma. D. The Coroner 10-somite embryo showing location of young blood islands on yolk-sac (From Patten, *Human Embryology*, courtesy of The Blakiston Company.)

veins cephalic to them gradually drop out altogether and all the placental blood passes through the liver (Figure II-13C, D).

Shunting Mechanisms in Embryonic Circulation. With the completion of this change in the umbilical circulation, the liver has become the common path of return for both of the original extra-embryonic circuits. This mounting volume of blood returning through the liver and reaching the heart by way of the developing inferior vena cava is, of course, a major portion of the cardiac intake during intra-uterine life. The fact that the original bilaterally symmetrical relations of these incoming vessels are shifted to the right side of the developing cardiac septa, as the caval system replaces the primitive cardinal system of vessels, is of vital importance in understanding the functioning of the developing heart. The right-left imbalance in cardiac intake thus

set up creates the necessity for compensatory shunting mechanisms (Patten, 1946). *On the intake side*, we shall see the shunt in the form of the series of interatrial communications which are maintained throughout fetal life. *On the output side*, the shunt is effected by the ductus arteriosus which persists until after birth. It is only when one realizes that the maintenance of intracardiac balance is as important to the fetus as it is to the adult, and comprehends the mechanisms which effect the balancing, that the sequence of events in the partitioning of the heart can be logically interpreted.

The First Embryonic Blood Corpuscles. While the heart and the main vascular channels of the embryo have been taking shape, changes leading toward the formation of the first blood corpuscles of the embryo are occurring in the yolk-sac (Sabin, 1922; Bloom and

Bartelmez, 1940). Connecting with the developing vitelline blood vessels in the splanchnopleure of the yolk-sac are prevascular cords of mesodermal cells, as yet not hollowed out. In these cellular cords are frequent knot-like enlargements, known as *blood islands* (Figure II-14A), containing not only cells which are destined to form vascular endothelium but also cells which will give rise to blood corpuscles. In the differentiation of a blood island the peripherally located cells become flattened and somewhat separated from the rest of the mass (Figure II-14B). Eventually they become arranged as a coherent investing layer, a single cell in thickness, and clearly endothelial in nature. Meanwhile, fluid accumulates inside the endothelium and the enclosed cells which were situated toward the center of the original mass become rounded and take on the characteristics of primitive blood corpuscles (Figure II-14B and C).

As the endothelial vesicles enlarge, they become confluent with similarly differentiating blood islands (Figure II-14C) with the resulting formation of a plexus of freely anastomosing endothelial tubes, the primordial capillary bed of the yolk-sac. When these

capillaries have attained open communication with the main vascular channels to and from the heart, everything is in readiness for the commencement of the embryonic circulation, for meanwhile the heart has developed a beat sufficiently effective to propel the blood.

The Three Arcs of Embryonic Circulation. By way of a simplified summary emphasizing its functional significance, the early embryonic vascular system can be resolved into three distinct sets of afferent and efferent channels. Each set of these main channels, with its interpolated capillary bed, can conveniently be called a *circulatory arc*. One of these arcs we may designate as *intra-embryonic*. In this arc, the blood pumped by the heart is distributed by the aortae to the embryonic body. Small branches from the aortae break up locally into capillaries which bring the blood into intimate relation with the developing tissues, facilitating the passing on to them of oxygen and food materials, and relieving them of the waste products of their metabolism. The blood is then collected by the cardinal veins and the other venous channels which later arise in association with them, and is returned to the heart.

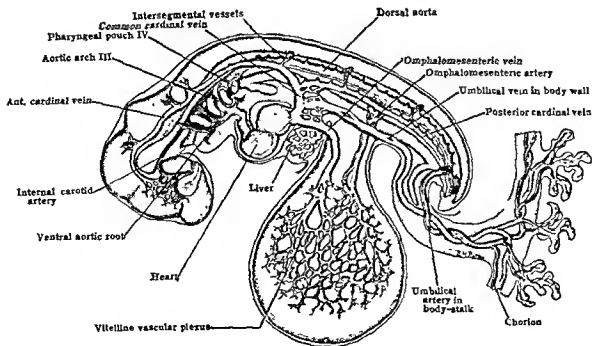


Figure II-15. Semischematic diagram to show basic vascular plan of human embryo at end of first month. For the sake of simplicity the paired vessels are shown only on side toward observer. (From Patten, *Human Embryology*, courtesy of The Blakiston Company.)

The other arcs are the *vitelline* which runs to the yolk-sac, and the *allantoic* or *umbilical*, to the chorion (Figure II-15). Both these arcs start within the embryo, for the heart serves as a common receiving and pumping station, and the aorta as a common distributing main, for all three of the circulatory arcs. But because their main vessels extend outside the body with their terminal ramifications in the extra-embryonic membranes, these latter arcs are ordinarily spoken of as extra-embryonic.

We see in the vitelline arc the strong imprint of phylogeny. The ancestral stock from which the higher mammalian types have evolved had a large yolk-sac well supplied with food material stored in advance by the mother. The development, in such forms, of a special circulatory arc by means of which this raw material for growth is absorbed and transported from the yolk-sac to the body of the embryo for utilization is exactly what one would expect. Higher mammals, although no longer dependent on food stored as yolk for their growth, still go through the inherited motions of forming a yolk-sac and a vitelline circulation.

The allantoic arc is phylogenetically less ancient than the vitelline. Instead of being a regressing mechanism, as is the vitelline arc, it reaches its greatest development in mammals. In young mammalian embryos, it is the means of projecting embryonic vessels onto the inner face of the chorionic vesicle, thereby bringing the embryonic blood sufficiently close to the uterine blood of the mother to facilitate the interchange of food, oxygen and waste materials. It is but natural that this extra-embryonic extension of the circulation should appear very early and carry a relatively large amount of blood. It is on this arc that the yolkless embryos of higher mammals are dependent for the metabolic interchanges without which their development would be impossible.

Beginning of the Circulation of Blood. It is a matter of considerable interest to know the approximate time of beginning of the circulation in man. No direct observations have been made but reasoning from condi-

tions known to exist in other embryos kept under continuous observation by tissue-culture methods (Goss, 1938, 1940, 1942), we can place the time of the first heart beats of the human embryo at about the end of the third week of development.

In chick embryos in which the first cardiac pulsations and the beginning of the circulation of blood have been observed and recorded by micromoving-pictures (Patten and Kramer, 1933; Patten, 1939, 1949), the first beats, although rhythmic in character, are not sustained and periods of pulsation are interspersed with quiescent periods. There is a considerable interval of time between the first contractions of the growing heart muscle and the beginning of the circulation of blood.

Meanwhile corpuscles are being formed in the blood islands of the yolk-sac and the venous channels leading to the heart contain fluid. At first this fluid is devoid of corpuscles but, just before the actual circulation of blood begins, a few corpuscles can be seen in the veins, freed from their parent cell clusters and shuttling back and forth with each heart beat. The heart has now apparently developed sufficient power to propel the blood, corpuscles are formed, and there is a fluid vehicle in the vessels. As soon as the gradually developing maze of small peripheral channels opens the connections between arteries and veins, a jerky progression of the corpuscles replaces their shuttling movement and the circulation of blood has commenced. If the sequence of events in the human embryo is comparable to that in the chick, it would be four or five days after the heart showed its first twitching before it set the blood in motion, probably some time late in the third week of development. Strong corroborative evidence that this actually is the time at which the blood begins to circulate is furnished by serial sections of young human embryos. Such specimens will begin to show blood corpuscles in the lumen of the heart during the latter part of the third week. Only by the pumping action of the embryonic heart could these corpuscles have been carried there from their place of origin on the yolk-sac.

THE CONVERSION OF THE PRIMITIVE TUBULAR HEART TO ITS DEFINITIVE, CHAMBERED CONDITION

To appreciate the significance of the changes which occur in the growing heart, one must have in mind the exigencies under which it develops. Starting as a simple tube, with the blood passing through it in an undivided stream, it must become converted into an elaborately valved, four-chambered organ, partitioned in the midline and pumping from its right side a pulmonary stream which is returned to the left side and pumped out again by way of the aorta as the systemic blood stream. And the heart cannot cease work for alteration, there can be no interruption in the current of blood it pumps to the growing embryo. This is but one phase of the matter. The pulmonary arc of the circulation cannot work up gradually to full functional activity because it is impossible for the lungs to take in air until after birth. Yet the pulmo-

nary circulation must, at the moment of birth, be ready to take over the entire responsibility of oxygenating the blood. Furthermore, in the early phases of development, the left side of the heart can receive but a small volume of blood from the lungs because no more can pass through them in their undeveloped condition. Yet it must be ready at the time of birth to pump through the myriad peripheral vessels of the systemic circulation the full blood stream received from the newly-functional lungs. These are some of the situations which must be faced before the heart can arrive at its adult condition. The manner in which they are met is doubly interesting because they seem at first sight so insurmountable.

One of the primary factors leading toward the early regional differentiation of the

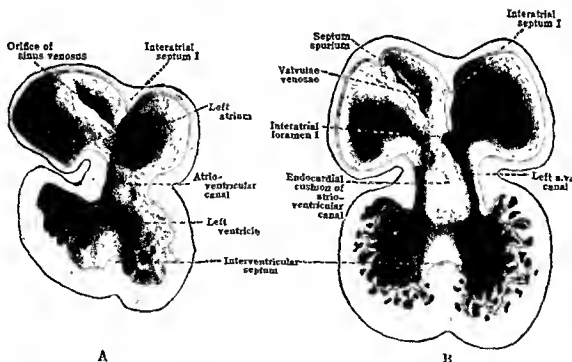


Figure 11-16 Semischematic drawings of interior of heart to show initial steps in its partitioning. A. Cardiac septa are represented at stage reached in human embryos early in fifth week of development. Note especially the primary relations of interatrial septum primum. Based on original reconstructions of the heart of a 3.7-mm. pig embryo, and on Tandler's reconstructions of corresponding stages of the human heart. B. Cardiac septa as they appear in human embryos of sixth week. Note restriction of interatrial foramen primum by growth of interatrial septum primum. Based on original reconstructions of the heart of 6-mm. pig embryo, on Born's reconstructions of rabbit heart, and Tandler's reconstructions of corresponding stages of the human heart. (From Patten, *Human Embryology*, courtesy of The Blakiston Company.)

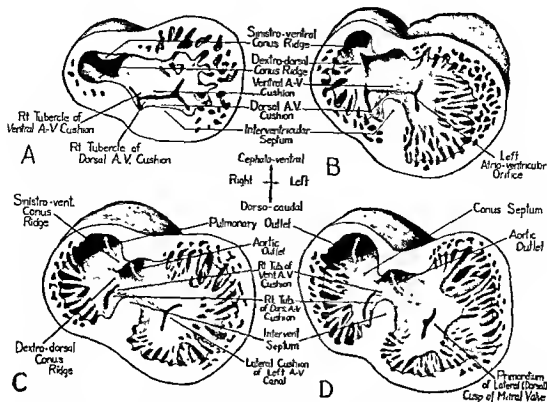


Figure II-17 Four stages in partitioning of atrioventricular canal. (After Kramer, *Am. J. Anat.*, Vol. 71, 1942.) The apex of the ventricle has been cut off and the heart is viewed from below. In this aspect, the relations of conus ridges to A-V canal cushions and to the upper part of interventricular septum are especially instructive.

heart is the rapid elongation of the primitive cardiac tube. The heart increases in length so much faster than the chamber in which it lies that it is first bent to the side and then twisted into a loop. Since the cephalic end of the heart is anchored in the body by the ventral aortic roots, and the caudal end by the great veins, it is the midportion of the cardiac tube which, in the bending process, undergoes the most extensive changes in position. This is facilitated by the early disappearance of the dorsal mesocardium which leaves the heart entirely free in its midregion.

During the period in which the cardiac loop is being formed, the primary regional divisions of the heart have, as we have seen, become clearly differentiated (Figure II-8). Almost from their earliest appearance, the atrium and the ventricle show external indications of the impending division of the heart into right and left sides. A distinct median furrow appears at the apex of the ventricular loop (Figures II-8D and E). The atrium, meanwhile, has undergone rapid dilation and bulges out on

either side of the midline (Figures II-8 and II-29). Its bilobed configuration is emphasized by the manner in which the truncus arteriosus compresses it midventrally.

Thus, by the end of the first month of development, the principal regional divisions of the heart are recognizable. Functionally, however, the heart is still acting as a simple contractile tube, with an undivided blood stream entering its sinoatrial end and being pumped out at its ventricular end.

Partitioning of the Atrium and Atrioventricular Canal. The basis of the partitioning of the heart into right and left sides is largely laid down during the second month of development, but the final phases of this division and the rerouting of blood streams involved cannot be completed until after birth when the placenta ceases to be the source of oxygen, and lung-breathing begins. In the separation of the primitive common atrium into right and left chambers, two septa are directly involved. These, on the basis of their sequential appearance, are commonly called

septum primum and septum secundum (Born, 1889; Tandler, 1912; Odgers, 1938, Patten, 1953). Starting as a crescentic ridge on the dorsocephalic part of the atrial wall, *septum primum* grows toward the atrioventricular canal (Figure II-16).

At about the same time that *septum primum* is making its appearance, the first indications of the impending division of the original common atrioventricular canal into a right and a left channel become evident. Two local thickenings, one dorsally, the other ventrally located, appear in the walls of the canal. These thickenings are the endocardial cushions of the atrioventricular canal. Each cushion consists of a plastic mass of embryonal connective tissue, of the type characteristically appearing in the developing heart at points where septa will fuse, or where elaborate connective-tissue structures, such as the cardiac valves, are destined to be molded. During the sixth week of development the dorsal and ventral cush-

ions are brought into contact with each other by their own growth, and fuse to form a common mass dividing the atrioventricular canal (Figures II-16 to II-18). There is then left between the concave margin of *septum primum* and the growing atrioventricular canal cushions a progressively diminishing opening known as the *interatrial foramen primum*, or *ostium primum* (Figures II-16B and II-18).

While these changes have been occurring, the sinus venosus has been shifted out of the midline so that it opens into the atrium to the right of the newly formed interatrial septum (Figure II-16). The heart is now in a critical stage of development. Its simple tubular form has been altered so that the four chambers characteristic of the adult heart are clearly recognizable. But there is as yet no division of the blood stream because there are still open communications from the right to the left side in both atrium and ventricle. A little

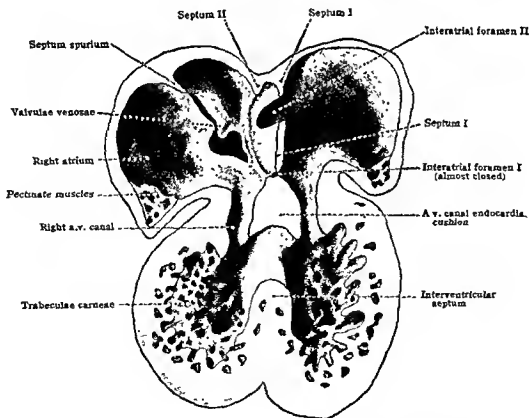


Figure II-18. Semischematic drawing of interior of heart to show start of interatrial septum secundum and appearance of interatrial foramen secundum in septum primum. Based on original reconstructions of the heart of a 9.4-mm. pig embryo and on Tandler's reconstructions of the heart of human embryos of seventh week. (From Patten, *Human Embryology*, courtesy of The Blakiston Company.)

further progress in the growth of the partitions, however, and the two sides of the heart would be completely separated. Were this to occur in the young embryo, the left side of the heart would become almost literally dry. An insignificant amount of blood from the undeveloped lungs is all that would enter it, for the sinus venosus into which systemic, portal, and placental currents all enter has, as we have seen, come to open on the right of the interatrial septum. The partitions in the ventricle and in the atrioventricular canal do progress rapidly to completion (Figures II-16, II-18, II-19 and II-20) but an interesting series of events takes place at the interatrial partition which assures that an adequate supply of blood will reach the left atrium and thence, the left ventricle.

Just when septum primum is about to fuse with the endocardial cushions of the atrioventricular canal, closing the interatrial foramen primum, a new opening is established. The more cephalic part of septum primum is resorbed* to form *interatrial foramen secundum*. The appearance of a second interatrial communication, just as the initial one is closing, is of fundamental significance because the constant presence of an interatrial communication makes it possible for the left atrium to receive, without interruption, a contribution from the blood entering the right atrium.

More than the atrial part of the heart is involved in this matter of balanced atrial intakes, for the atrioventricular canal is divided by the 10-mm. stage, and at about the 16- to 17-mm. stage the interventricular septum separates the

right and left ventricles from each other. After these partitions are completed, if the atrial intakes were unbalanced, the ventricular intakes would inevitably be correspondingly disturbed. That this is a matter of more than theoretical importance is clearly shown by the conspicuously defective development of the left side of the heart which is encountered when, as occasionally happens, abnormal development prematurely closes or markedly narrows the interatrial communication of the fetal heart (Patten, 1938; see also Figure VI-23).

About the time the secondary interatrial opening is formed in septum primum, another septum begins to develop. Like septum primum, *septum secundum* is crescentic in shape, but the open part of the crescent is directed more caudally and dorsally—toward the inferior part of the sinus inlet rather than toward the atrioventricular canal as was the case with septum primum. The more cephalic tip of septum secundum lies along the cephalodorsal wall of the atrium (Figure II-18). The more caudal tip merges with the endocardial cushions of the atrioventricular canal just to the right of the line of fusion formed by interatrial septum primum in the closure of primary interatrial communication (Figure II-29D). There is, as development progresses, a consolidation of interatrial septum primum and septum secundum to form that part of the definitive interatrial septum which fuses with the partition dividing the atrioventricular canal (Figure II-29E and F). There is, moreover, some interdependence in the growth of these septa at this point. If the atrioventricular cushions fail to fuse, interatrial septum primum will tend to remain undeveloped on the atrial side of this defect. If the canal cushions and septum primum are defective, septum secundum follows their lead and fails to grow into the characteristically shaped opening in the interatrial septum just above the point where it should have fused with the partition of the atrioventricular canal. Such a defect (Figures VI-7 to VI-12) is usually spoken of as a persistent interatrial foramen primum, although this designation does not take adequate account of a possible under-

* Interatrial foramen secundum develops first in the form of multiple small perforations which secondarily coalesce to establish a single sizable opening situated cephalodorsally in septum primum. Occasionally some of the initial small openings may arise in septum primum outside of the usual territory, and persist independently without being incorporated into the main interatrial foramen secundum. If such accessory openings are low in their location, they may appear in the fully formed heart in the part of septum primum which lies opposite the subsequently formed foramen ovale in septum secundum and serves as its valve (Figure II-52C and D). Such ectopic openings are particularly interesting from the theoretical standpoint in that they represent a developmental defect which is the result of excess resorption, instead of being in any sense a "developmental arrest."

lying factor in defective growth of the atrio-ventricular canal cushions, nor of the secondary deficiency in the growth of the caudal limb of septum secundum which seems to follow if septum primum has not laid the basis for its extension.

As septum secundum grows, its concave margin for a time cuts progressively farther into the atrial lumen; but septum secundum is not destined to become a complete partition. Its extension gradually ceases, leaving a characteristic oval aperture which is the *foramen ovale* (Figures II-19, II-20, and II-29). The margin of septum secundum thus constitutes

what in adult anatomy is called the *limbus* or *annulus fossae ovalis*.

The relations of septum primum to the oval foramen persisting in septum secundum are of vital importance. The secondary opening in septum primum is formed so near the cephalic wall of the atrium that the unresorbed lower part of septum primum lies as a loose flap, covering on its left atrial side the oval opening in septum secundum (Figures II-19 and II-20). In this position it acts as a one-way valve, permitting the filling of the left atrium from the right but effectively shutting off return flow. In the fully formed fetal heart

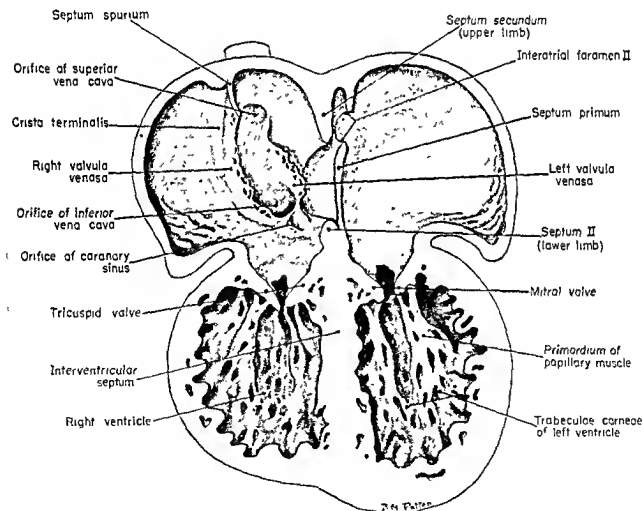


Figure II-19. Schematic drawing to show the internal configuration of the heart in human embryos of the third month. At this stage, resorption has begun to involve the valvulae venosae and septum spurium, as indicated by the many small perforations in their margins. Note the way the left venous valve is coming to lie against septum secundum with which it is already beginning to fuse. It usually leaves no recognizable traces in the adult, but occasionally delicate lace-like remains of it can be seen adherent to septum secundum and, more rarely, extending on to the valvula foraminis ovalis (cf. Figures II-20 and VI-24-26). (From Patten, *Foundations of Embryology*, courtesy of the McGraw-Hill Book Company, Inc.)

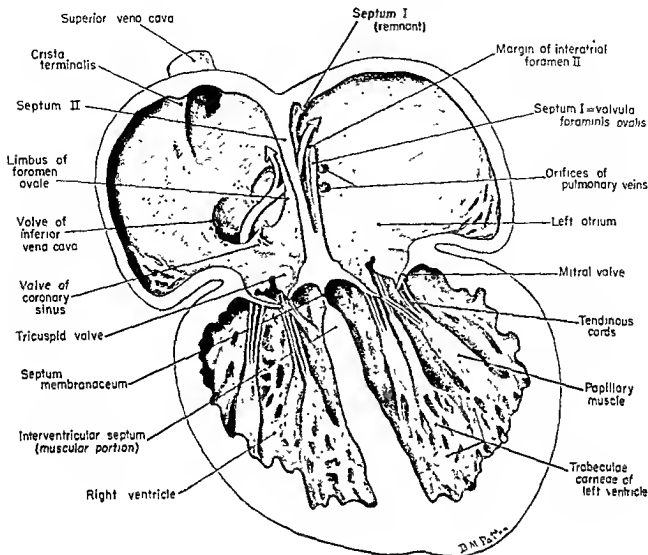


Figure II-20. Schematic drawing to show interrelations of septum primum and septum secundum during latter part of fetal life. Note especially the way in which the lower part of septum primum is situated, so that it acts as a one-way valve at the oval foramen in septum secundum. The split arrow indicates the way a considerable part of the blood from the inferior vena cava passes through the foramen ovale to the left atrium while the remainder eddies back into the right atrium to mingle with the blood being returned by way of the superior vena cava. (From Patten, *Foundations of Embryology*, courtesy of the McGraw-Hill Book Company, Inc.)

this flap is commonly known as the *valvula foraminis ovalis* rather than by its embryologic name, septum primum.

Primary Muscular Part of the Interventricular Septum. Indications of the division of the primitive ventricle into right and left chambers appear at about the same time that the first interatrial septum becomes recognizable. Early in the second month the primary muscular part of the *interventricular septum* appears at the apex of the ventricular bend, leaving an *interventricular foramen* between its crescentic margin and the bottom of the partition in

the atrioventricular canal (Figure II-16).

In its earliest stages the *interventricular septum* appears to be little more than a ridge of *trabeculae carneae* (Streeter, 1948). When it is carefully reconstructed, a fine flexible probe can be passed through it from one ventricle to the other by way of the *intertrabecular spaces*. As development progresses the *trabeculae* tend to become more compactly arranged, to form a relatively solid myocardial mass. Occasionally, however, this consolidation may not be complete, with the resultant persistence of small tortuous *interventricular*

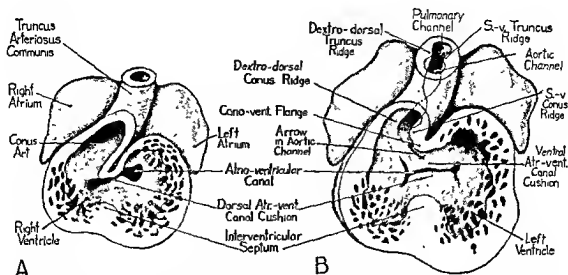


Figure II-21. Semischematic dissections of developing heart, viewed in frontal aspect to show relations of importance in establishing aortic and pulmonary outlets. (After Kramer, *Am. J. Anat.*, Vol. 71, 1942.)

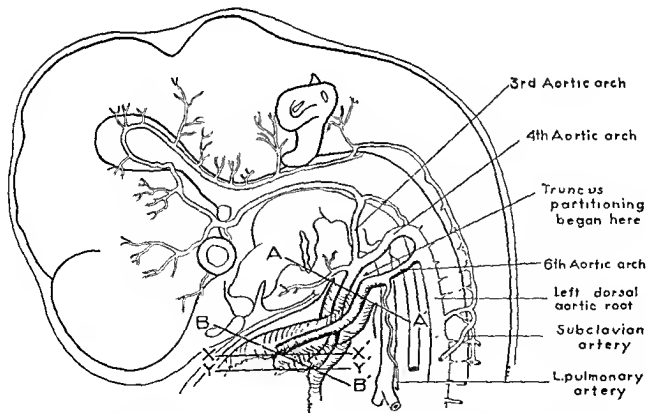


Figure II-22. Diagram showing the spiral course of the truncocoanal partitioning, based on conditions in embryos of about 14 mm. (early in seventh week). The line A-A' indicates the level of the sections diagrammed in Figure II-23, the line B-B' indicates the level of the sections diagrammed in Figure II-24, the lines X-X' and Y-Y' indicate the locations of the photomicrographs appearing as Figure II-25, A and B.

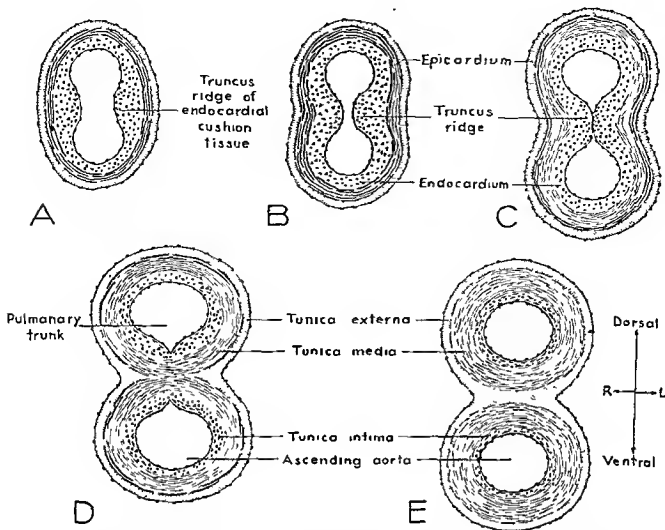


Figure II-23. Schematic diagrams showing the partitioning of the truncus arteriosus to form the ascending aorta and the pulmonary trunk. The relations are depicted as they would appear at the level of the line A-A' in Figure II-22.

openings in the main muscular portion of the septum (Cf. Figure VI-34).

The interventricular septum is usually described as growing toward the atrioventricular canal cushions and thus progressively reducing the size of the interventricular foramen. This serves well enough to emphasize the relative changes seen in comparing hearts of different ages (Figures II-16 and II-18), but it expresses in somewhat oversimplified terms what has actually happened. Actually it would be more nearly correct to say that the ventricular chambers on either side of the septum expand, leaving the septum projecting relatively farther into the enlarged ventricular lumen and causing the interventricular foramen to appear smaller in comparison with the size of the septum.

The interventricular foramen, instead of having its closure delayed until after birth as is the case in the atrium, is closed surprisingly early. Normally all traces of the opening will have disappeared by the end of the seventh week (embryos of 17 to 19 mm.). The final closure of the interventricular foramen is not, however, accomplished by the main muscular part of the septum. The last remaining opening is closed by a composite mass of connective tissue derived in part from the connective-tissue margin of the interventricular septum itself, in part from the base of the endocardial cushions forming the partition in the atrioventricular canal, and in part from the conus ridges.

Partitioning of the Truncus Arteriosus and Formation of the Aortic and Pulmonary

Valves. The involvement of the conus ridges in the closure of the interventricular foramen makes it necessary to take up at this point the partitioning of the truncus arteriosus, for the conus ridges are merely prolongations into the ventricle of the ridges which fuse to divide the truncus into aortic and pulmonary channels. The partitioning of the truncus begins distally between the roots of the fourth and sixth aortic arches and continues back through the truncus toward the ventricles. The division is effected by the growth of a pair of ridges composed of the same type of plastic young connective tissue which we saw constituting the atrioventricular canal cushions (Frazer, 1917, Spitzer, 1919-21, 1922, Odgers, 1939; Kramer, 1942). As these ridges grow, they cut more and more deeply into the lumen of the truncus (Figure II-23A and B) and finally meet to form a complete partition (Figure II-23C and E), separating an aortic channel leading into the fourth aortic arches and a pulmonary channel leading into the sixth aortic arches (Figure II-22). The fact that

these truncus ridges pursue a spiral course as they grow toward the ventricles accounts for the way the ascending aorta and the main pulmonary trunk twist around each other as they emerge from the ventricles (Figure III-1). The same spiraling brings the aortic channel around into a position to receive the blood pumped by the left ventricle, and the pulmonary channel into a position to receive the right ventricular output (Figures II-21B, II-22 and II-27).

The level at which the aortic and pulmonary valves develop may be regarded as the line of demarcation between the truncus arteriosus and the tapering ventricular outlet called the conus. Here, there is a local elaboration of the endocardial cushion tissue of the truncus ridges. In the walls of both the aorta and the pulmonary trunk three small pads of plastic young connective tissue develop and bulge into the lumen (Figures II-24D and E and II-25B). The two pads in either vessel which lie adjacent to the point of fusion of the ridges appear to develop as local

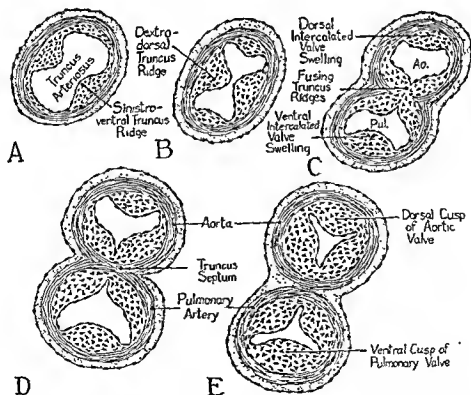


Figure II-21. Schematic cross-sectional diagrams to explain partitioning of truncus arteriosus. The relations are depicted as they would appear at the level of the developing semilunar valves (line B-B' in Figure II-22). (After Kramer, *Am. J. Anat.*, Vol. 71, 1942.)

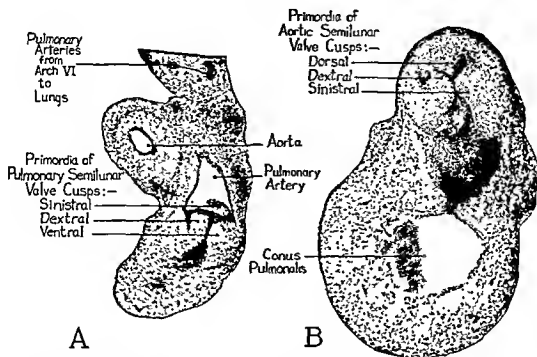


Figure II-25. Photomicrographs of sections through developing aortic and pulmonary valves of a 13-mm. human embryo. The level of the section shown in A is indicated by the line X-X', and that in B by the line Y-Y' in Figure II-22. (After Kramer, *Am. J. Anat.*, Vol. 71, 1942.)

enlargements of the ridge tissue. The primordia of the dorsal valve of the aorta and of the ventral valve of the pulmonary trunk are formed by independent local growth centers in the intima opposite the points of fusion of the ridges. For this reason, the primordia of these cusps have been aptly described by Kramer (1942) as the dorsal and ventral *intercalated valve swellings* (Figure II-24C). Gradually each of these buttonlike masses of intimal connective tissue becomes molded into one of the cusps of the semilunar valves of the aorta or of the pulmonary artery. During the later stages of development there is further rotation of the aorta and the pulmonary trunk about each other so that the aortic valve cusp which arose from the dorsal intercalated valve swelling is carried around into a dextral position, and the pulmonary valve cusp which arose from the ventral intercalated cushion is carried into a sinistral position (cf. Figure II-24E with Figure II-28).

Closing of the Interventricular Foramen and Attainment of Definitive Relations at the Ventricular Outlets. On the ventricular side of the aortic and pulmonary valves, ridges of the same type which appeared in the truncus

are continued into the funnel-shaped ventricular outlet under the name of the *conus ridges* (Figures II-21B and II-27). These conus ridges follow a direct continuation of the spiral course of the truncus ridges. The rate of turn of the spiral is such that it brings the conus ridges in line with the crest of the interventricular septum and reduces, from above, the size of the interventricular foramen (Figure II-26). Local enlargements (tubercles) of the right margin of the endocardial cushions of the atrioventricular canals also crowd into the diminishing interventricular foramen (Figures II-17 and II-27). Thus the final closure of the interventricular foramen is accomplished, not by the growth of the primary crescentic muscular septum, but by a plastic mass of connective tissue derived mostly from the conus ridges and from the right tubercles of the atrioventricular canal cushions, with a small contribution from the connective tissue that caps the crest of the muscular part of the interventricular septum. This composite mass of connective tissue completing the interventricular septum is at first rather bulky and loosely organized (Figure II-29E). As the septal cusps of the atrioventricular valves are

molded, and as the connective tissue itself becomes more highly differentiated, the interventricular septum at this point of final closure gradually becomes a thin fibrous sheet (Figure II-29F), known as the *membranous part of the interventricular septum (pars membranacea septi)*.

When one reviews mentally all the various developmental processes involved in the partitioning of the ventricles and the division of the truncus arteriosus into aortic and pulmonary trunks, it is not surprising that the region of the ventricular outlets is one of the commonest sites of developmental disturbances. It is not enough that each component part, such as the truncus septum, must be laid down according to a certain pattern. Other components, such as the main muscular part of the interventricular septum and the atrioventricular canal cushions, starting elsewhere in the growing heart, must also follow their appointed course and attain the appropriate degree of development in order to be joined, one with the other, at just the right place. Moreover, all the component parts must meet, not only at the right place, but also at the right time, for if one is unduly delayed, the associated parts will develop beyond their early condition of plasticity which makes possible the necessary fusions. This matter of the "timing" of developmental processes is, incidentally, one of the most easily overlooked, yet most vitally important, of the

factors underlying malformations, and one concerning which we need much more precise information than we possess at present.

The developmental malformations of the heart are to be dealt with in detail in Chapter VI. It is not, therefore, pertinent here to do more than call attention to the special vulnerability of this particular region and the general way in which some of the growth processes here being considered may be disturbed. For example, unequal division of the truncus arteriosus as a result of misplaced truncus ridges may produce an unduly narrow pulmonary trunk with a correspondingly overlarge aorta. Conversely, if the malposition of the truncus ridges is in the reverse direction, one is confronted with an aortic stenosis and a large pulmonary trunk. In both such cases, the conal prolongation of the truncus septum is out of its normal position. It is only natural, therefore, that when one of its component primordia is displaced, the septum membranaceum is likely to remain incomplete. Such a correlated sequence of events is what presumably underlies "the large aorta arising astride of an interventricular septal defect" which is such a characteristic part of the picture in the so-called tetralogy of Fallot.

The foregoing examples merely suggest the kind of developmental disturbances which involve the relations of the aortic and pulmonary outlets of the ventricles. A recent extensive

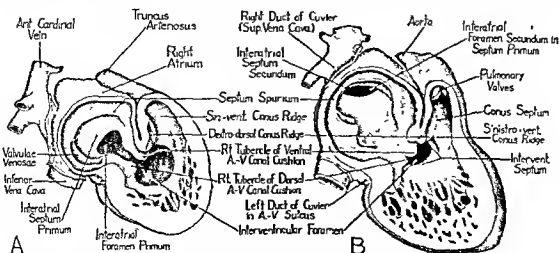


Figure II-26. Schematic lateral directions to show relations of various septa in the developing heart. (Kramer-Patten. From Patten, *Human Embryology*, courtesy of The Blakiston Company.)

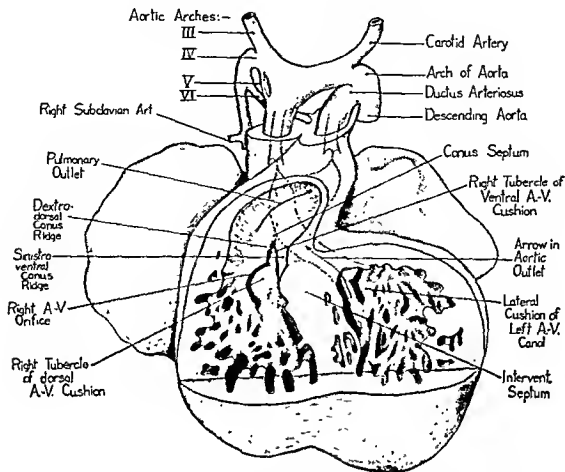


Figure II-27 Reconstruction of heart of a 13-mm. embryo, opened to show relations of conal septa to interventricular septum and the atrioventricular canal cushions. (After Kramer, *Am. J. Anat.*, Vol. 71, 1942.)

and exceedingly valuable study by Shaner (1949) emphasizes the manner in which early maldevelopment of the endocardial cushions of the atrioventricular canal may be an underlying cause in malformations of the truncus region. The frequency with which these and related malformations are encountered make it particularly important to be thoroughly familiar with the normal development and topography of this region of the heart.

The accompanying diagrams (Figure II-28), showing the normal relations of the aortic and pulmonary outlets, were drawn from the unconventional but very effective approach used in some of Taussig's (1947) illustrations portraying the conditions in pulmonary stenosis. The locations of the aortic and pulmonary outlets are projected on a cross section of the underlying ventricles in such a manner that their relations to the septum membranaceum are especially emphasized. In A,

which represents schematically the relations in fetal hearts, it will be seen that the aortic outlet is not rotated as far around behind the pulmonary outlet as is usually the case in adult hearts. It should, however, be noted that in adult hearts there is considerable individual variation in these relations and any configuration between the characteristic fetal and adult relations here diagrammed should probably be regarded as within normal limits. Another point of interest brought out by these diagrams is the fact, often overlooked, that the right and left ventricular walls of the fetal heart are of approximately equal thickness. The marked preponderance of the left ventricular wall in adult hearts is a postnatal characteristic acquired gradually during the first three or four years of life (Cruss, 1921).

In following the sequence of events in the partitioning of the heart, consideration of many other concurrent developmental changes

was postponed for the sake of coherence. It is now, therefore, necessary to take up such subjects as the manner in which the atrioventricular valves are formed, the changes which occurred in the sinus venosus while the atrium and ventricle were being subdivided; the way nerves and vessels reach the growing heart; and something of the origin of the sinoventricular conduction system.

Atrioventricular Valves and Papillary Muscles. At the point where the right and left atrioventricular canals open into the ventricles there are early indications of the establishment of valves. From the partition which divided the originally single atrioventricular canal, and from the outer walls on each side, masses of tissue in the shape of thick, blunt flaps project toward the ventricle (Figure II-18). It is these masses of a primitive type of connective tissue similar to that of the endocardial cushions of the canal which later become differentiated into the flaps of the adult atrioventricular valves. The processes involved are gradual alterations in shape, accompanied by slow histogenetic modifications of the character of the component tissues. Changes of this type do not lend themselves readily to

description by ages or stages, and we must seek rather to grasp their major trends.

One of the essential features of any cardiac valve is the *fibrous annulus* to which its leaflets are attached and which reinforces the orifice against overdistension as the pressure builds up behind closed valves. At first the undivided atrioventricular orifice of the young embryonic heart is encircled by tissue which is almost entirely developing cardiac muscle. There is only a very thin outer epicardial layer, consisting of little more than mesothelium, and an endothelial layer which is just beginning to be backed by a scanty amount of connective tissue that has not yet progressed to the stage of fiber formation (Figure II-29A and B). When the atrioventricular canal is divided into right and left channels by the fusion of endocardial cushion masses (Figure II-29C and D), the foundation is laid for the mesial portion of each of the atrioventricular rings. Concurrently, the epicardial connective tissue begins to cut into the myocardium at the atrioventricular sulcus. By the end of the eighth week (Figure II-29E), it has met the endocardial tissue so that all around the atrioventricular constriction the myocardium of the

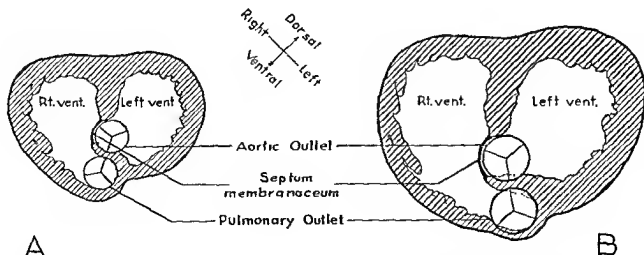


Figure II-28 Diagrams to show the relations of the aortic and pulmonary outlets to the membranous portion of the interventricular septum. The outlets and their semilunar valves are projected onto a schematized cross section of the underlying ventricles in a manner suggested by some of Taubig's illustrations. A. Fetal relations when right and left ventricular walls are of equal thickness. B. Relations as seen in a child of four years or older, when the left ventricular wall has attained its adult degree of preponderance and there has been some further rotational change in the positions of the aortic and pulmonary outlets. Note that the diagrams are oriented on the basis of the division of the heart into right and left sides by the interventricular septum, as one might hold the excised heart in his hand. For the position of the heart in the body, turn the page so the arrow representing the dorsoventral axis is vertical.

ventricle is cut off from the myocardium of the atrium by connective tissue. There remain, connecting atrial and ventricular myocardium, only slender fascicles of young cardiac muscle fibers which extend from the floor of the right atrium into the dorsal limb of the crescentic muscular part of the interventricular septum and thence along its crest. There they bifurcate to send fibers into each ventricular wall. This persisting group of myocardial fibers is destined to be differentiated into the atrioventricular bundle (bundle of His) and its main branches. These will receive further consideration when the sinoventricular conduction system, of which they are a part, is discussed.

The connective tissue growth, which tends to separate atrial from ventricular muscle, establishes the primordium of the so-called cardiac skeleton. Around each of the now separate atrioventricular orifices, the plastic young connective tissue begins to differentiate into the circularly disposed collagenous fiber bundles that form the tricuspid and the mitral annuli. Toward the lumen similar young connective tissue is molded into flange-like projections which constitute the primordia of the atrioventricular valves (Figures 11-29D-E and 11-37). From the way in which the two atrioventricular canal cushions fuse with each other to divide the atrioventricular canal, it is evident that the primordial tissue for the septal leaf of the tricuspid valve and for the medial leaf of the mitral valve must arise, in part, from the dorsal and, in part, from the ventral endocardial cushion of the atrioventricular canal. This is a point of importance in understanding the notching of these valves which is so generally seen in connection with defects low down in the atrial septum (Figure VI-7). In such instances of persistence of interatrial foramen primum there is apparently a co-existing tendency for the atrioventricular canal cushions to lag somewhat in their growth and fusion, and it is this tendency which leaves its record in the form of the characteristic notching of the valves.

As the flanges which constitute the valve primordia become extended, the trabeculated myocardium is carried out on their ventricular

surfaces. Then the developing valve is composed of loosely organized young connective tissue continuous with the muscular trabeculae of the heart wall on its ventricular face (Figure 11-29E). In the final molding of the valves, the muscle on their ventricular face undergoes retraction and regression, so that the basis of the valve flaps becomes entirely connective tissue. At the same time, the muscle pulls away from the part of the trabeculae directly adherent to the valve and thus leaves only slender fibrous strands which are the fore-runners of the *tendinous cords* (Figure 11-29F). The basal portions of these same trabeculae thereby become relatively thickened to constitute the *papillary muscles*.

The latest phases of valve development involve the histologic maturing of its component parts. In the annulus are developed heavy interlacing bundles of collagenous fibers which constitute the valve ring and at the same time send out strands which anchor the base of the valve leaflets to the annulus. The tendinous cords come to be constituted by parallel bundles of collagenous fibers anchored in perimysial tissue of the papillary muscles. Last of all to make its appearance is the strongly developed meshwork of slender elastic fibers which are so characteristically interlaced with the finer collagenous bundles of the atrial faces of the adult valves. In the light of the retraction of the myocardium from its early association with the valve primordium, the occasional presence of a few rudimentary muscle fibers in the subendothelial connective tissue of the valvular endocardium is readily understandable. The curious ill-defined histologic picture these fibers often present in the adult has led to their being confused with the smooth muscle cells that occur sporadically in the endocardial tissue in many places in the heart. Under favorable conditions, however, the cardiac character of these rudimentary muscle elements of the ventricular surface of the atrioventricular valves can be clearly seen. Throughout all the changes we have been considering, the endothelium at all times constitutes an unbroken covering of the developing valves themselves and their associated tendinous cords and papillary muscles.

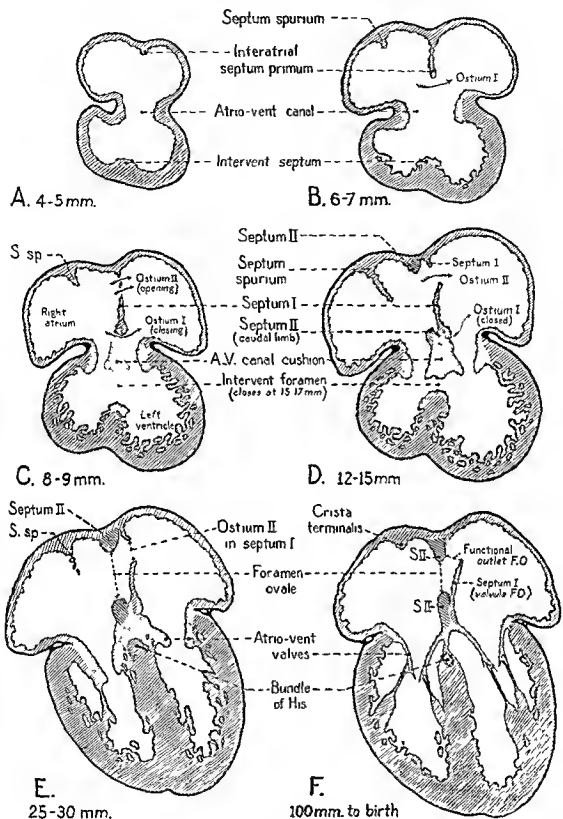


Figure 11-29. Sectional plans of embryonic heart in frontal plane, showing extent of growth of various cardiac septa at several stages of development. These diagrams give specifically for the human embryo a more precise picture of the rate of progress of partitioning than do the preceding schematic drawings. Stippled areas in the diagrams indicate distribution of endocardial cushion-tissue; muscle is shown in diagonal hatching, and epicardium in solid black. The lightly-stippled areas in atrioventricular canal in B and C indicate location of dorsal and ventral endocardial cushions of atrioventricular canal before they have grown sufficiently to fuse with each other in the plane of the diagram. (Modified from Patten, *Am. J. Path.*, 14:135, 1938.)

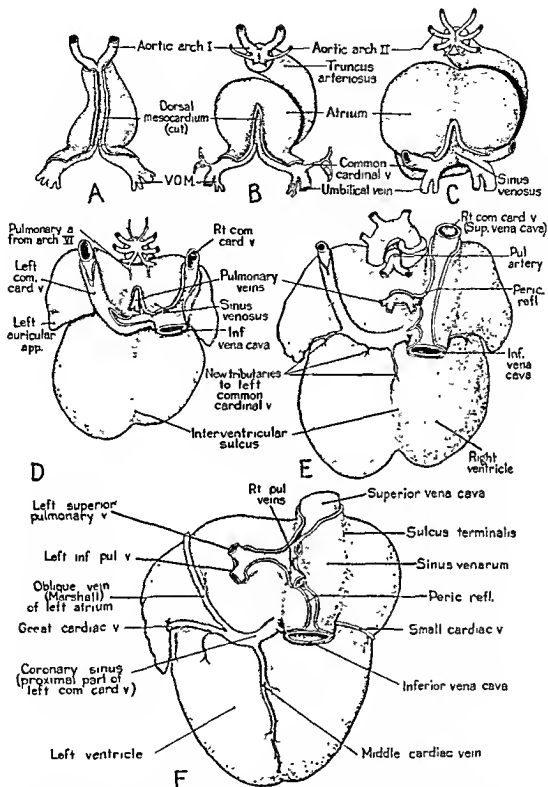


Figure 11-30. Six stages in the development of the heart, drawn in dorsal aspect to show changing relations of sinus venosus and great veins entering heart. A. Two and one-half weeks (8-10 somites). B. Three weeks (12-14 somites). C. Three and one-half weeks (17-19 somites). D. Five weeks (6-8 mm. crown-rump length). E. Eighth week (embryos of about 25 mm.). F. 11 weeks (embryos of about 60 mm.). (From Patten, *Human Embryology*, courtesy of The Blakiston Company.)

Changes in the Sinus Region. The so-called sinus venosus of the embryonic heart has not been as carefully studied as it merits. Moreover, the fact that the composition of the sinus venosus is so radically different at various ages has led to considerable looseness in its description. In early stages, what is commonly called the sinus venosus is merely the region of confluence of the great veins which bring the blood back to the caudal end of the primitive tubular heart (Figure II-30C). The sinus venosus as it appears in somewhat older hearts is still essentially the region of confluence of the entering veins, but additional mesial fusion of the primary omphalomesenteric vessels has occurred so that the original sinus territory

has been increased, and the opening into it of the newly formed caval inlet further changes its configuration (Figure II-30D). Concurrently, the epimyocardium comes to invest the sinus endocardium more and more completely (Figure II-30C-E). At the same time, also, the opening of the sinus into the atrium is shifted out of the midline so that it comes to lie on the right side of the developing interatrial septum (Figure II-16). These changes, taken in conjunction with the rapid expansion of the atrium, in increasingly intimate association with which the sinus develops, soon combine to give the sinus somewhat the shape of a lopsided "U" bulging out on the dorsal wall of the atrium (Figure II-30D). The limbs of

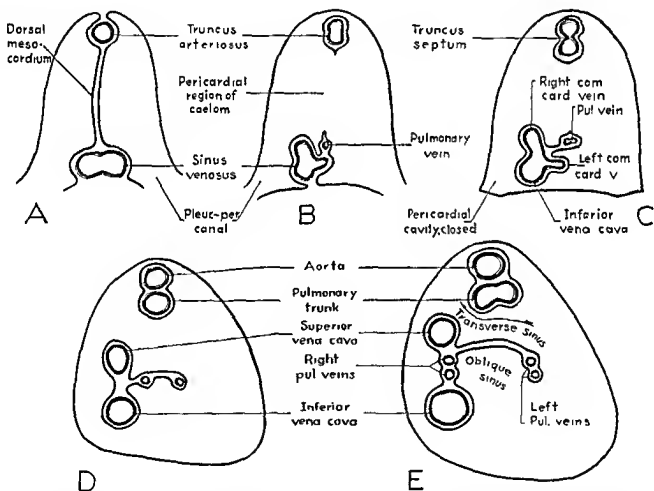


Figure II-31. Schematic diagrams showing a series of stages in the establishing of the adult pattern of pericardial reflections. Each plan represents a ventral view of the layout of the opened pericardial cavity from which the heart has been removed. The orifices outlined in red are the arterial outlets, those outlined in blue are venous inlets. The heavy black lines represent the cut pericardial reflections about the vessels and peripherally, the cut parietal pericardium. These figures should be carefully compared with the dorsal views of a series of removed hearts showing comparable stages (Figure II-30).

the "U," into which the right and left common cardinal veins enter, are usually spoken of as the "horns of the sinus."

The early U-shaped condition of the sinus does not long persist. With the formation of the left innominate vein as a new transverse anastomosis between the right and left anterior cardinals (Figure II-12D), more and more blood is shunted to the right so that the right common cardinal progressively increases in size, a change indicative of its conversion into the superior vena cava (Figure II-30E and F). At the same time the left common cardinal, toward the heart from the anastomosis, becomes correspondingly smaller. Where it crosses the dorsal wall of the left atrium, if it persists in a reduced state into adult life, it is known as the *oblique vein of the left atrium* or *vein of Marshall* (Figure II-30F). As the blood from its original cephalic drainage area is reduced, the most proximal part of the left common cardinal which lies across the dorsal wall of the heart in the atrioventricular sulcus begins to acquire new tributaries from the heart itself. When this has occurred, we may well call it by its adult name, *coronary sinus* (Figure II-30E and F). The original left horn of the sinus venosus, in this process, becomes greatly reduced in relative size and what remains of it merges with the proximal part of the left common cardinal vein in the formation of the coronary sinus (Figure II-30F).

While the right common cardinal vein has thus been relatively increased by the innominate shunt to form the superior vena cava, the inferior cava has increased even more strikingly in size. The recirculating of systemic (Figure II-12) and portal and placental venous returns (Figure II-13) through the liver to converge in the inferior vena cava is, as we have seen, the underlying reason for this relatively tremendous growth. The inevitable result of the increase in blood volume returning through the two venae cavae is the marked relative enlargement of the original right horn of the sinus venosus to form the *sinus venarum* (Figure II-30F).

As both the right horn of the sinus venosus and the right atrium grow in size, the external

boundaries between the two regions become progressively less conspicuous. Mesially the border of sinus territory comes to merge with the external depression opposite the interatrial septa; on the right a shallow groove, known as the *sulcus terminalis*, marks its boundaries. The extent to which the old boundaries become thus inconspicuous has led to the not-too-accurate statement that "the sinus venosus is absorbed into the dorsal wall of the right atrium."

Internally, in young hearts, the opening of the sinus venosus into the right atrium is flanked by a pair of well developed valves, the *valvulae venosae* (Figure II-16). At the cephalic end of the sinus orifice the two valves merge into a flange-like structure which projects deep into the right atrium from its dorso-cephalic wall. This structure is known as the *septum spurium* because, although it is very prominent in the hearts of two- to three-month-old fetuses, it later undergoes regression without playing any part in the partitioning of the right and left atrial chambers. Its reduction is accomplished by a resorptive process starting simultaneously in many areas, so that when it is partially reduced it is likely to have a lace-like appearance. The anomalous meshwork of strands sometimes are found in adult hearts attached along the crista terminalis and the margins of the eustachian and thebesian valves, named "Chiari's net" (Figures VI-21 and 25), represents vestiges of the right valvula venosa and its continuation as the septum spurium, which have persisted when the process of resorption by which they are normally molded has remained incomplete.

Concurrently with the blending of the right sinus horn into the dorsal wall of the right atrium externally, there are even more striking changes internally. The progressive resorption of the valvulae venosae and the septum spurium and the partial incorporation of the sinus into the expanding right atrium gradually result in the superior and inferior cavae and the coronary sinus all opening independently (Figures II-19 and II-20). The reduced septum spurium is now represented only by the crista terminalis and the much re-

duced remains of the right venous valve are converted into the highly variable *eustachian valve* of the inferior vena cava and *thebesian valve* of the coronary sinus. The frequency with which small perforations appear in both these valves is indicative of the nature of the resorptive process by which the redundant young valvulae venosae are, so to speak, "cut down to size."

Although not usually conspicuous, lace-like remnants of the lower part of the reduced left venous valve will occasionally be seen in adult hearts lying closely adherent to septum II near the caval inlet and sometimes extending across the limbus fossae ovalis to adhere to the valvula foraminis ovalis (Figure VI-26).

PERICARDIAL RELATIONS

The pericardial, pleural, and peritoneal cavities of the adult develop as subdivisions of the coelom of the embryo. The embryonic coelomic cavities are primarily paired, arising on each side of the midline by splitting of the lateral plate of mesoderm into an outer (somatic) layer and an inner (splanchnic) layer, with the coelom between. The part of the coelom which is destined to be segregated as the pericardial cavity appears very early in development (Figures II-1 and II-2). At the time the cardiac primordia take shape, the original paired condition of the coelom in the pericardial region still persists (Figure II-3A and B). As the young tubular heart is molded, the splanchnic mesodermal layers which form its epimyocardium meet in the midventral line to complete the investment of the endocardial primordia. Where they come in contact with each other beneath the heart, they immediately break through so that the originally separate right and left coelomic chambers become confluent ventral to the heart (Figure II-3C). For a time the newly established tubular heart is suspended beneath the pharynx by a double layer of splanchnic mesoderm, known as the dorsal mesocardium, which continues to separate the original coelomic chambers dorsally (Figures II-3C and D, and II-31A). As the cardiac tube lengthens and begins to bend (Figure II-4), the dorsal mesocardium breaks through and leaves the heart suspended by its two ends in the pericardial portion of the coelom. Caudally the pericardial chamber still communicates on either side with the rest of the coelom (Figure II-7) by way of the pleuropericardial canals (Figure II-31A and B). With the clo-

sure of these canals, the pericardial chamber is established as an isolated cavity (Figure II-31C through E).

In the light of the foregoing events, it should be apparent that the outermost layer of the heart has remained directly continuous with the lining of the pericardial chamber at two points: (1) where the truncus arteriosus is attached beneath the pharynx and (2) where the sinus venosus is suspended by a persisting part of the dorsal mesocardium at the caudal end of the pericardial chamber (Figures II-7 and II-31B and C). In other words, it is at these two areas that the *epicardium* (*visceral pericardium*) is continuous with the *parietal pericardium*. The changes which take place as development progresses beyond this basic condition are the obvious ones entailed by the division of the truncus into aorta and pulmonary trunk, and by increase in the number of separate venous orifices as the sinus venosus is incorporated into the dorsal wall of the right atrium and the pulmonary veins are formed.

The changes which occur at the truncus are so simple that they call for no comment. The changes in the pericardial reflections at the sinus end of the heart can best be understood by comparing the diagrammatic plots of Figure II-31 with the dorsal views of removed hearts drawn to show the development of the sinus venosus (Figure II-30). In these drawings the cut edges of the pericardium are shown where they were reflected from the parietal walls of the pericardial cavity to become the epicardial (*visceral pericardial*) layer of the heart. In Figure II-31 the heavy black lines about the appropriately colored

vascular orifices represent the same reflections, as they would appear on the dorsal wall of the pericardial cavity from which the heart has been removed. As the sinus venosus is incorporated into the growing right atrium, the originally single orifice (Figure II-31A) is replaced by separate orifices for the superior and inferior venae cavae (Figure II-31B through D). At the same time the left common cardinal vein (future coronary sinus) acquires its own opening into the heart (Figure II-31C) and the fold of mesocardium which surrounded it at early stages (Figure II-30D) disappears, as the coronary sinus becomes closely applied to the heart wall (Figure II-30E and F).

While these changes have been going on in the main vessels entering the sinus venosus, the pulmonary veins have been taking shape. The primary venous plexus which is organized in connection with the growing lung-buds originally drains into channels which connect with the anterior cardinal veins. Gradually, however, there is developed a new medial collecting channel that enters the atrial region dorsally. This channel, at first a single median vein collecting blood by a tributary vein from each lung, reaches the left atrium by passing between the reflected pericardial layers which represent persisting portions of the dorsal mesocardium (Figures II-30D and II-31B). As the heart grows, the single median portion of the pulmonary venous channels is incorporated into the atrial wall so that its main right and left tributaries come to empty by two separate orifices (Figures II-30E and II-31C). As the right and left orifices become progressively more widely separated from each other, the mesocardial fold enclosing them is pulled out transversely (Figure II-

31C and D). Ultimately this process of eliminating the proximal portions of the pulmonary veins continues until it involves the first main bifurcation on the right and on the left, so that there come to be two right and two left pulmonary vein orifices (Figure II-31E).

The changes in the manner of entrance of the pulmonary veins just described leave a transversely placed reflection of the pericardium with a caudal extension on the left enclosing the two left pulmonary veins, and a longer caudal extension on the right enclosing the two right pulmonary veins and the inferior vena cava. The bay-like pericardial space so bounded is known as the *oblique sinus* (Figures II-31E and III-6). Concurrently the *transverse sinus* is being delimited. When the midportion of the dorsal mesocardium is resorbed, the two sides of the pericardial cavity are placed in open communication dorsal to the heart (Figures II-7 and II-31B). This communication is the *transverse sinus* in primordial form. As development progresses, the cardiac tube is bent into a tight loop and its receiving and discharging ends are brought relatively closer together. In this process the original pericardial communication dorsal to the heart is narrowed and its caudal boundary is remodeled by the changes which we have just been following in the sinus region (Figures II-30 and II-31). These changes, however, merely alter the detailed configuration of the transverse sinus and in no way change its original essential relations as a communication from one side of the pericardial cavity to the other, dorsal to the heart. It is, of course, this relationship which places it in sharp contrast with the oblique sinus which is essentially a bay, or pocket, ending blindly behind the heart (Figures II-31E and III-6).

VESSELS AND NERVES OF THE HEART

The Coronary Circulation. The origin of the main coronary veins has been considered in connection with the formation of the coronary sinus into which they drain. The coronary arteries arise from the aorta during the seventh week, shortly after it has been partitioned off in the division of the truncus arteriosus. Care-

ful study of serial sections is necessary to identify the newly formed coronary arteries for they are very small when they first appear in embryos of 14- to 15-mm. crown-rump length, and their delicate endothelial lining is easily missed in the loose young connective tissue which they traverse in their origin,

above the primordial valve pads. Once established, the coronary arteries enlarge quite rapidly and it is not difficult to trace their course (Figure II-32). The right coronary emerges from the aorta to traverse the groove between the pulmonary conus of the right ventricle and the right auricular appendage, and then courses along the coronary sulcus to the diaphragmatic surface of the heart, giving off at intervals branches which enter the myocardium. The left coronary artery emerges between the base of the pulmonary trunk and the left auricular appendage to send its main branch along the interventricular sulcus and give off a smaller, circumflex branch in the left atrioventricular sulcus.

The smaller branches of the coronary arteries, when they enter the myocardium, break up into an extraordinarily rich bed of capillaries investing the developing muscle fibers. Most of the blood entering this plexus is returned by way of the coronary veins. Some of the small vessels, however, make connection with the endothelially-lined spaces among the trabeculae. In young hearts, these *intertrabecular spaces* are relatively large. As the trabeculae become more robust, the spaces are greatly reduced so that, in the deeper parts of the myocardium, they come to be of about the order of magnitude of sinusoids. When this has occurred, it becomes virtually impossible, in sections, to tell which small endothelially-lined space was derived from the ingrowth of sprouts from the invading coronary vessels, and which was derived by reduction of the original intertrabecular spaces. The so-called *venae minimae cordis*, the orifices of which can be found to open at many places into the cardiac cavities, really represent reduced intertrabecular spaces communicating with the maze of endothelially-lined crevices of similar origin which, in turn, receive blood from connections with the coronary circulation. Only by a realization of the nature of this unorthodox vascular relationship can one acquire an understanding of some of the abnormalities encountered in the coronary circulation. Particularly is this the case in communications such as those sometimes seen in an aberrant coronary (or coronary branch)

which enlarges one of its primary connections, with the intertrabecular spaces of one of the ventricles, usually the right. Sizable channels of this type have been misdescribed as "aneurysms" originating in an aortic sinus and extending through the myocardium to emerge in the pulmonary cone of the right ventricle.

The Nerves to the Heart. From the functional standpoint, the details of the nerve supply of even the adult heart are still inadequately known. Its double innervation from sympathetic and parasympathetic sources is, of course, quite familiar, together with the antagonistic accelerator and depressor effects of these two sets of nerves on heart rate. But as they approach the heart, sympathetic and parasympathetic fibers become intricately mixed in the so-called cardiac plexus, and the terminal distribution of fibers within the heart itself and their precise functions still offer challenging problems. Even less satisfactory is our knowledge of the embryologic development of these two categories of nerves supplying the heart. We do, however, have some basic data as a starting point (Streeter, 1912; Shaner, 1930; Licata, 1954). The parasympathetic fibers from the vagus are easier to follow in early stages than are the sympathetic fibers. The primordial ganglionic cell cluster of the vagus becomes recognizable as a vaguely defined mass of neuroblasts of neural crest origin early in the fourth week. In the fifth week the jugular ganglion and the nodose ganglion with its component of neuroblasts of epibranchial origin are clearly recognizable. By the sixth week, growing motor nerve fibers from neuroblasts within the brain stem, and sensory fibers from neuroblasts in the ganglia have extended to form a strongly developed visceral branch of the vagus nerve following along each side of the trachea and esophagus. Among these growing nerve fibers are many cells, some of which are destined to be neurilemma-sheath cells; others, which are neuroblasts migrating along the developing nerve, are destined to form ultimately the terminal ganglion cells that give rise to the second-order neurons of the two-neuron parasympathetic efferent chain. At cardiac level, delicate branches turn off and follow along



the developing aortic and pulmonary trunks toward the main mass of the heart. In these branches, also, are many migrating neuroblasts along with the growing nerve fibers. By the seventh week the main vagal branches to the developing cardiac plexus are clearly recognizable (Figure 11-33).

The preganglionic sympathetic fibers concerned in relaying impulses to the postganglionic fibers which enter the cardiac plexus arise from cell bodies, most of which are located in the first four thoracic segments of the spinal cord. Some arise in the fifth thoracic segment and possibly a few also in the sixth. These fibers enter the ganglia of the prevertebral sympathetic chain and pass cephalad to one of the cervical, or to the first thoracic ganglion. There they synapse with the second-order (postganglionic) neurons, the fibers of which constitute the cardiac nerves. The neuroblasts from which these postganglionic fibers are formed have come into the chain ganglia from the spinal ganglia at corresponding levels. These cells travel along the developing spinal nerve and the ramus communicans to aggregate in their characteristic prevertebral locations. It is probable that they are joined by other neuroblasts which arise in the mantle layer of the developing spinal cord and migrate out along the ventral nerve roots, so that the cells from both sources move together along the course of the ramus communicans. The ganglia of the sympathetic chain which originate in this manner do not make their appearance as early as the ganglia of the vagus nerve, but by the seventh week they are read-

ily recognizable and the postganglionic fibers arising from their neuroblasts have begun to mingle with the vagus fibers extending to the heart (Figure 11-33). Thus, before the end of the second month it is possible to recognize quite clearly both the sympathetic and parasympathetic components of the cardiac plexus.

It is quite probable that better technical methods will permit us to recognize migrating neuroblasts moving into the cardiac region somewhat earlier than they have been demonstrated by the studies at present available. It seems unlikely, however, that even the well-organized fibrocellular strands, which we can readily recognize as developing nerves by our present routine staining methods, have as yet begun to function in the transmission of impulses. It is highly significant that, in forms which can be secured for study under experimental conditions, the pulsation of the heart has commenced and the blood has been effectively set in motion in the embryonic circulation, long before even the first neuroblasts from the vagus can be seen moving out toward the territory in which they later take part in the formation of the cardiac plexus. This fact, taken in conjunction with the autonomous rhythm maintained by excised embryonic hearts, leaves no room to doubt the primary myogenic character of the embryonic heart beat. We would seem fully justified in concluding that when the nerves grow in and make connections with the heart that is already beating, their effect is limited to a secondarily superimposed regulation of its rate of pulsation.

THE SINOVENTRICULAR CONDUCTION SYSTEM

Some of the experimental work which has been done on the initiation of the beat and its propagation in young embryonic hearts

(Patten and Kramer, 1933; Armstrong, 1935; Goss, 1938, 1940, 1942; Copenhagen, 1945; Patten, 1949, 1956) provides the best possible

← Figure 11-32 Photomicrographs showing early steps in the establishing of the coronary arteries. A. Section of heart of 14.8-mm. embryo passing through the aortic outlet. Photo, X 35, from human embryo EH 314. B. Section of aortic outlet of 19-mm. embryo. X 60 from EH 358. The plane of cutting is unusually fortunate in showing both coronary orifices in the same section. C. Section of aortic outlet and part of wall of left ventricle of 31.5-mm. embryo. X 60 from EH 377.

(All embryos from the University of Michigan Embryological Collection. The collaboration of Dr. Richard Licata in the preparation of this illustration is gratefully acknowledged.)

Abbreviations: ADB, anterior descending branch of left coronary artery; EB, branch of coronary artery turning to course superficially in the epicardium; MB, branch of coronary artery entering the myocardium; LCA, left coronary artery; RCA, right coronary artery; SV, primordial semilunar valves of aorta.

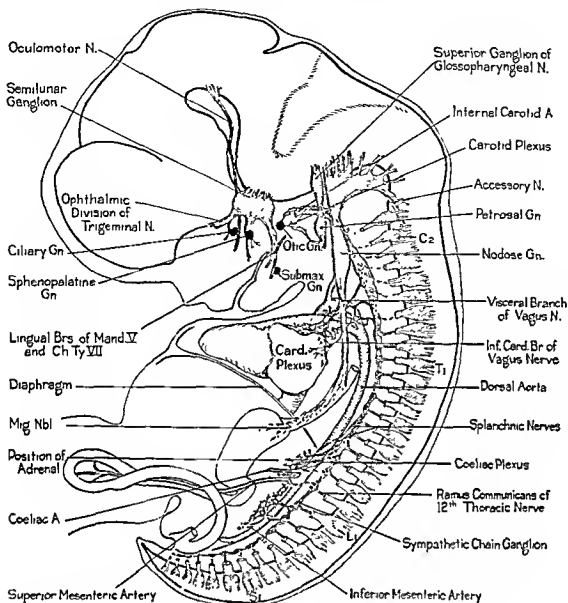


Figure 11-33 The autonomic nervous system of a human embryo (18 mm.) of the seventh week (From Patten, *Human Embryology*, redrawn after Streeter, courtesy of The Blakiston Co.)

basis for understanding the so-called sino-ventricular conduction system of the adult heart. In discussing the formation of the primary tubular embryonic heart, it was emphasized that the various regions were formed in cephalo-caudal sequence, as the closing of the foregut permitted the paired cardiac primordia to meet in the midline. Thus the first part of the heart to be formed is the conoventricular portion. This is followed by the formation of the atrium and, last of all, by the establishing of the sinus venosus.

Contractile activity begins to involve the cardiac regions in the same sequence in which

they are formed. The first contractions appear in the conoventricular myocardium, before fusion of the paired primordia is completed in the atrium, and while the sinus venosus is represented only by endocardial primordia which are still widely separated from each other and which are entirely devoid of myocardial covering. The initial rate of pulsation in the primitive ventricle is relatively slow. When fusion of the cardiac primordia has extended caudad to establish the atrium and this part of the cardiac tube begins to pulsate, the rate for the entire heart is increased. Transecting the beating heart clearly demonstrates

which part of the heart is dominant in the control of its rate (Patten and Kramer, 1933; Paff, 1936). In such experiments, the isolated atrium continues to beat at essentially the rate exhibited by the entire heart before it was cut. The isolated ventricular part drops down to a much slower rate, approximating that characteristic for the early phases of development when the ventricle was the only part of the heart beating (Figure II-34). Similar cutting experiments carried out at a later stage, after fusion of the cardiac primordia has established the sinus venosus caudal to the atrium, show that sinus myocardium has a faster rate than atrial myocardium. The picture presented by three isolated segments, cut from the same tubular heart, each beating at its own characteristic rate, is most dramatic (Figure II-35). It means that there is a gradient in the contraction rate of the myocardial primordia, with the intrinsic rate of pulsation becoming progressively higher as the myocardial samples are excised from the more and more caudal parts of the cardiac tube. During development, then, there is not "a" pacemaker

in the heart but rather a succession of pace-making zones, new areas that are added behind the ones already established show a progressively faster inherent rhythm and assume, in turn, domination of the slower-beating regions previously laid down. Thus the slower rate of beating of the ventricle is accelerated when faster-beating atrial tissue is added behind it, setting the pace for atrioventricular contraction waves. When, a little later, the still-faster-beating sinus venosus is added behind the atrium, it assumes the pacemaking function and sino-atrio-ventricular contraction waves are established. In this manner, as the cardiac tube itself differentiates, it is traversed by peristaltoid contraction waves initiated in what is, at the moment, its most caudal part. Since this most caudal part is at the same time the blood-receiving end of the heart, it would be difficult to postulate a more simple and efficient means of propelling blood through a pump that is still valveless.

By zigzag cutting experiments, it is possible to demonstrate that the entire embryonic myocardium at these early stages is effective

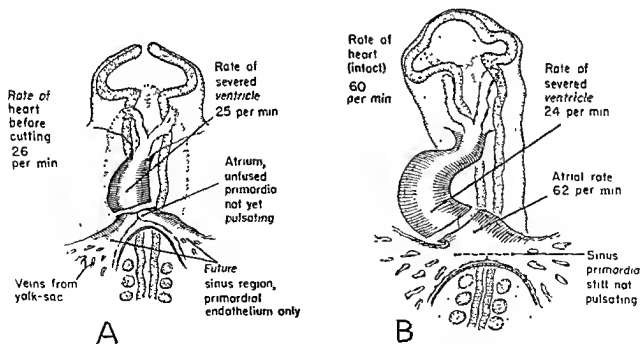


Figure II-34. Diagrams showing the locations of cuts made in living hearts of young embryos. A. Embryos of 10-12 somites. At this stage only the ventricle is pulsating, and cutting it away from the nonactive atrium has no appreciable effect on its rate. B. Embryos of 13-15 somites. By this stage the atrium has begun to pulsate, and in the intact heart acts as a pacemaker. Transection between atrium and ventricle shows the atrium maintaining essentially the rate of the intact heart, whereas the ventricle drops back to approximately the same slow rate it exhibited before the atrium became active and drove the ventricle at its own faster rate. (From Patten, *Univ. Michigan Med. Bull.*, 22:1-21, 1956)

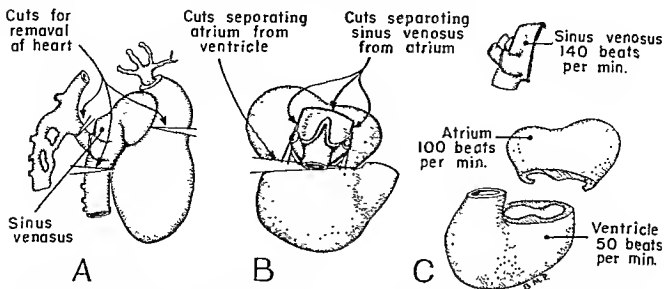


Figure II-35. Diagrams showing the location of cuts made in the living heart of a 4-day chick embryo to demonstrate the relative pulsation rates of the myocardium from different regions. A. Cuts for the removal of the heart. B. Cuts to separate sinus, atrium, and ventricle. C. The parts of the heart as isolated. The rates indicated are representative of the findings in such experiments, rather than specific for any particular case. (From Patten, *Univ. of Michigan Med. Bull.*, 22:1-21, 1936.)

in propagating the beat from the faster- to the slower-beating parts of the heart. Moreover, it is even possible, by carefully planned placing of interdigitating cuts, to make the impulses travel through muscle areas in a radically different direction from that which they normally traverse (Figure II-36). Such experiments vividly emphasize the conductive capacity of embryonic cardiac muscle and make it seem only natural that certain retained and modified tracts of it come to serve as the path of propagation of beats in adult hearts. In this connection it may be noted that, by employing adequate amplification, it is possible to secure electrocardiographic records from embryonic hearts still in the primitive tubular stage (Hoff, Kramer, DuBois and Patten, 1939). These tracings change progressively in character as the cardiac tube is lengthened. Well before the sinoventricular conduction system has been histologically differentiated, the embryonic myocardium yields polyphasic tracings essentially similar to those characteristic of the adult heart.

The details of the steps by which the sinoventricular conduction system is differentiated are far from adequately known. Certain of the major points, however, seem reasonably clear (Shaner, 1929; Walls, 1947; Patten,

1956). In discussing the formation of the fibrous rings of the atrioventricular orifices, it was pointed out that originally the atrial myocardium and the ventricular myocardium are broadly continuous throughout the entire circumference of the atrioventricular constriction (Figure II-29A through C). Gradually the epicardial and endocardial connective tissues encroach on the myocardium at the atrioventricular sulcus and ultimately interrupt the broad connection between atrial and ventricular muscle (Figure II-37A through C). The separation is rapidly completed peripherally around the sulcus, but there persists a connecting fascicle of muscle fibers from the dorsomedial part of the floor of the right atrium (Figure III-26), penetrating the fibrous base of the heart (Figure III-19) and extending along the crest of the primary muscular portion of the interventricular septum (Figure III-22). This is the *atrioventricular bundle (bundle of His)*. Like the young cardiac muscle from which it arises, it retains its capacity for transmitting the impulse to contract and ultimately becomes one of the critically important parts of the sinoventricular conduction system of the adult heart.

Traced into the ventricular myocardium, the main atrioventricular bundle bifurcates

and sends branches, the *right and left bundle branches* (Figures III-26 and III-27), along the septal walls of the two ventricles. These branches recurve in the lateral walls of ventricles and break up into richly branching strands of atypical cardiac muscle (the *Pur-*

kinje fibers, Figure III-28) which lie close beneath the ventricular endocardium. If one recalls the manner in which the ventricles of the *embryonic heart grow*, in effect ballooning out on either side of the *interventricular septum*, one may regard the atrioventricular

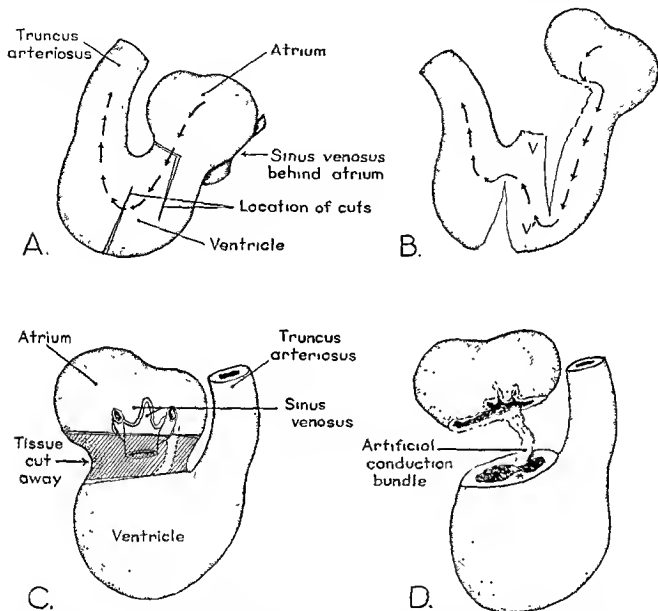


Figure II-36. Cutting experiments illustrating the conductive properties of embryonic cardiac muscle. The excised hearts were kept alive at body temperature in oxygenated Locke-Lewis solution for study and micro-mov-ing-picture recording of their action before and after experimental incisions.

A. Ventral view of heart removed from three and one-half day chick embryo. The arrows show the general direction in which the wave of contraction traversed the heart before the cuts were made.

B. Same heart diagrammed in A after making cuts in the locations there indicated. Note especially that the placing of the cuts is such that in the part of the ventricle V-V the beat is propagated in practically the reverse of its normal direction.

C. Dorsal view of heart removed from four-day chick.

D. Four-day heart with "artificial conduction bundle" made by cutting away the tissue in the regions indicated by diagonal hatching in C. Note that the artificial bundle was made by leaving a strand of muscle in the ventral part of the heart wall in a region as far as possible from that in which the His bundle later appears. The asterisk on the cut surface indicates the region where the His bundle would have been differentiated at a considerably later period of development.

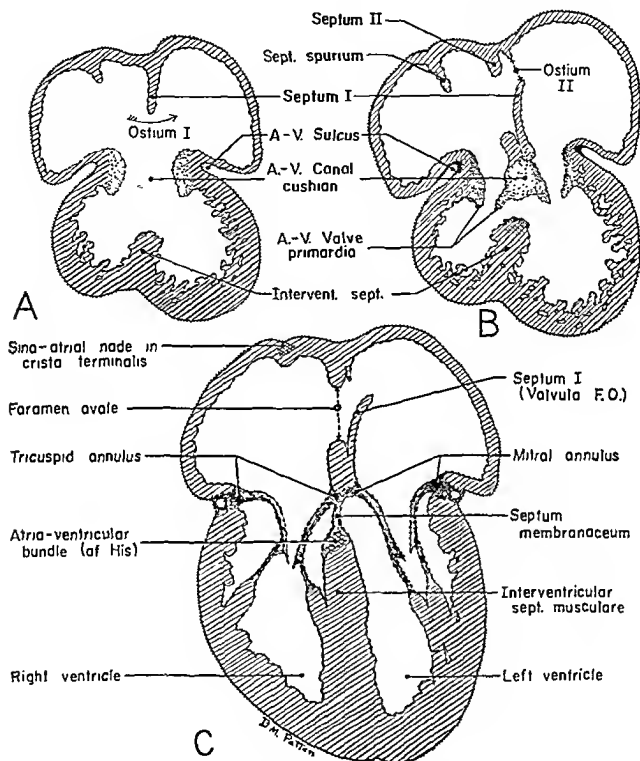


Figure 11-37. Diagrams illustrating how the development of the connective tissue of the "cardiac skeleton" separates the ventricular from the atrial myocardium with which it was originally directly continuous throughout the entire circumference of the atrioventricular groove. The mitral and tricuspid annuli are the parts most directly involved in this process. Scheme: myocardium, diagonally hatched; endocardial cushion tissue, stippled, connective tissue, line-shaded. (From Patten, *Univ. Michigan Med. Bull.*, 22:1-21, 1950.)

bundle and its right and left branches and their ramifications as representing a sort of primary core of embryonic cardiac muscle. The bundle is all that remains of the original extensive connection between atrium and ventricle, and the branches and their terminal ramifications are, so to speak, dragged out along the lines of expansion of the ventricular chambers. As will be brought out in the next chapter (Chapter III), all the parts of the sinoventricular conduction system are essentially cardiac muscle, although each part of the system has its own peculiar histologic characteristics.

The remaining parts of the sinoventricular conduction system are the *sinoatrial* and *atrioventricular nodes*. In the adult heart the sinoatrial node lies in the shallow sulcus where the inferior vena cava enters the right atrium (Figure III-25). In the formation of this region a considerable portion of the right horn of the sinus venosus has been incorporated in the dorsal wall of the right atrium, so that the sinoatrial node represents myocardium which was originally associated with the sinus horn. This is the most caudal part of the myocardial primordium and, in accordance with the cephalocaudal gradient in contraction rate, it is the most rapidly pulsating. It is therefore quite logical that, once it has been established, we should find it retaining its dominance over the contraction rate of the heart as a whole and becoming its adult pacemaking center.

The steps in the formation of the atrioventricular node are less well known and can be outlined only tentatively on the basis of present information. It seems probable, however,

that it should be regarded as starting its development as the counterpart, on the left sinus horn, of the sinoatrial node on the right. Young embryonic hearts appear to have, for a time, bilaterally symmetrical pacemaking areas located, one on either side, where the common cardinal veins enter the horns of the sinus venosus. Some adult reptilian hearts, moreover, appear to have retained this condition of paired sinus pacemakers. It will be recalled that with the shifting of the sinus venosus to the right, the left common cardinal is pulled far to the right (Figure II-30D through F). Thus, myocardial tissue, originally lying at the junction of the left common cardinal vein with the left sinus horn, could well be carried along with the positional changes involved in the conversion of left common cardinal and left sinus horn into the coronary sinus (Figure II-38). The adult location of the atrioventricular node in the floor of the right atrium close to the inlet of the coronary sinus (Figure III-25) is consistent with this tentative interpretation of its developmental history. This concept of the two nodes as originally symmetrical structures may also make it easier to understand why all the many careful attempts to trace connections from the sinoatrial to the atrioventricular node have so far proved unsuccessful. Just how the contractile impulse passes from the sinoatrial to atrioventricular nodes, and how the sinoatrial node came to take over the dominant role in the pacemaking function from its original partner, are some of the most challenging unsolved problems in basic cardiac physiology at the present time.

THE CHANGES IN CIRCULATION FOLLOWING BIRTH

All the steps in the partitioning of the embryonic heart lead gradually toward the final adult condition in which the heart is completely divided into right and left sides. Yet, from the nature of its living conditions, it is not possible for the fetus *in utero* fully to attain the adult type of circulation. The plan of the completely divided circulation is predicated on lung-breathing. In the adult the right side of the heart receives the blood re-

turning from a circuit of the body and pumps it to the lungs where it is relieved of carbon dioxide and acquires a fresh supply of oxygen. The left side of the heart receives the blood that has just passed through the lungs and pumps it again through ramifying channels to all the tissues of the body. In the fetus the function of respiration is carried out in the placenta, by interchange with the maternal blood circulating through the uterus.

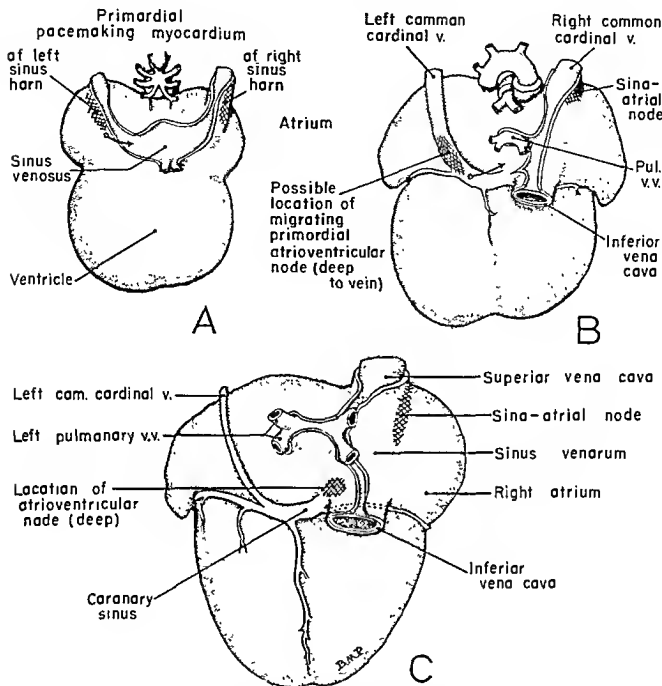


Figure 11-38 Dorsal views of the embryonic heart to show the pulling around of the left horn of the sinus venosus during development. The cross-hatched areas on the right indicate the known positional changes of the sinoatrial node. The cross-hatched areas on the left in A and B indicate possible positional changes in the atrioventricular node, on the hypothesis that it originates as the bilaterally symmetrical mate of the sinoatrial node. (From Patten, *U'mc Michigan Med. Bull.*, 22 1-21, 1936.)

The lungs, although they are fully formed and ready to function in the last two months of fetal life, cannot actually begin their work until after birth. The radical change, which must inevitably take place immediately following birth, in the manner in which the blood is oxygenated has led to a widespread belief that there must be revolutionary

changes throughout the cardiovascular system. It is true, as we shall see directly, that there are radical changes in the volume of blood passing through the vessels supplying such organs as the lungs and the kidneys. However, as the embryology of the circulatory system has been studied more closely from a functional angle, it is becoming increasingly

clear that the heart itself develops in such a manner that the pumping load on its different parts always remains nicely balanced during the changes in vascular pattern that occur during fetal life. Moreover, the very mechanisms which maintain this intracardiac balance during prenatal life are perfectly adapted to insure the transition to postnatal conditions without the sudden overloading of any of the cardiac chambers.

Course and Balance of Blood Flow in the Fetal Heart. To understand the changes in circulation which are so smoothly accomplished at the time of birth, it is necessary to keep in mind how the way for them has been prepared during intra-uterine life. In the foregoing account of the development of the interatrial septal complex, it was emphasized that at no time were the atria completely separated from each other. One will recall a succession of three morphologically distinct interatrial communications: the first, inferior to septum primum; the second, in septum primum, and the final one, the foramen ovale in septum secundum. This permits the left atrium, throughout prenatal life, to receive a contribution of blood from the inferior vena cava and the right atrium by a transseptal flow which compensates for the relatively small amount of blood entering the left atrium of the young embryo by way of the pulmonary circuit, and thereby maintains an approximate balance of intake into the right and left sides of the heart.

The precise manner in which this transseptal flow occurs, and where and to what extent the various blood streams of the fetal circulation are mixed within the heart, have long been subject to controversy. Most of the early conclusions were based on such circumstantial evidence as dimensions of orifices and positions of septa and valves. The critical factors of pressure and volume of flow have remained largely a matter of inference, pending the working out of the technically difficult problems incident to handling living fetuses by methods which would not unduly distort their normal physiologic activities. The brilliant work of Sir Joseph Barcroft and his colleagues (1941) went far toward putting

some of these old controversies in proper perspective. Working with fetal lambs, their first approach was through the quantitative analysis of blood samples drawn from various critical parts of the circulation. The oxygen concentration of such samples gives important evidence as to the mixing of the currents that actually takes place in the living heart. Later work, involving the collaboration of Barclay, Franklin and Prichard (1944) utilized serial x-ray photography following injection of opaque material into the blood stream at various points. This method gave further evidence regarding the course followed by some of the important blood currents.

Later (1949, 1954), Wegelius and Lind, working in Stockholm, successfully applied angiocardigraphic techniques to the study of living human fetuses. By using electronic intensification, they were able to obtain a sufficiently brilliant image on the fluoroscopic screen to permit its being photographically recorded on motion-picture film. Such records have furnished us with exceedingly valuable evidence as to the relative volume of the major circulatory arcs in the fetus. By carrying out similar observations on the newborn just before and just after the beginning of respiration, equally vivid records have been secured showing the changes in the pulmonary and in the renal circulation at the time of birth.

The results of these studies by newer methods have forced the revision of some of the inferences earlier workers had made from the observation of structural conditions in fixed material. For example, injections of the fetal blood vessels in the last trimester of pregnancy, followed by making of corrosion preparations, show the vessels of the lungs to be strikingly well developed (Figure 11-40A). As I have emphasized in my own earlier publications, it is natural to infer from such studies that these vessels might be expected to carry, in life, a blood volume consonant with their size as seen in injected specimens. But angiocardigraphic studies of living fetuses, made by injecting contrast medium through the umbilical vein, show the vessels

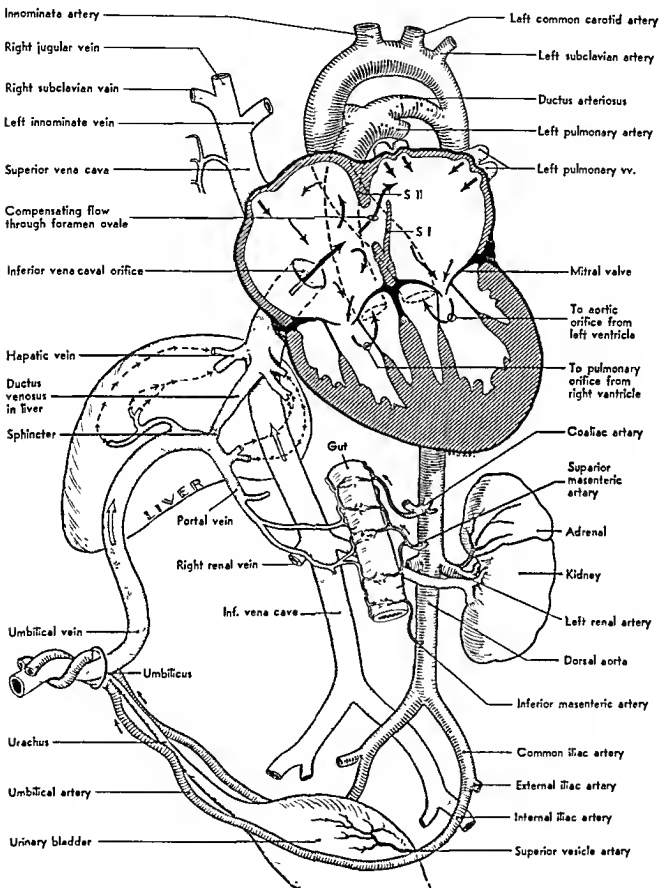


Figure 11-39 Diagrammatic plan of fetal circulation just before birth. (From Patten, *Foundations of Embryology*, courtesy of the McGraw-Hill Book Company.)

to the lungs carrying a less active circulation than their size would lead one to anticipate (Figure II-41). In marked contrast to such venous injections is the picture obtained by retrograde injections through the umbilical arteries. In these injections the pressure is raised above normal levels in order to force the contrast medium against aortic flow. When this is done, the angiocardigrams show the blood going into the pulmonary vessels with the conspicuousness one would expect from the study of preparations made by injection-corrosion techniques (*cf.* Figures II-40A and II-40B). Such retrograde injections clearly confirm the findings in morphologic studies which showed that long before birth the pulmonary vessels are well formed and of generous size. It is equally apparent, however, that under normal intrauterine conditions these

vessels are carrying a minute-volume of blood far below their potential capacity. This condition could be influenced by mechanical factors such as compression of spirally arranged arteries in the uninflated lungs, as maintained by Reynolds (1956), or by peripheral resistance to blood flow offered by the somewhat collapsed capillary bed of the uninflated lung. The sluggish flow through the pulmonary vessels could, to some extent, also be the result of vasoconstriction maintained by the small arteries and arterioles of the lungs prior to the initiation of respiratory activity. It seems not unlikely that all of these factors are involved. That the restriction of prenatal pulmonary flow is not caused solely by the mechanical compression of the capillaries is suggested by conditions in the kidneys. Here, although no spiral arterioles are involved and no inflation

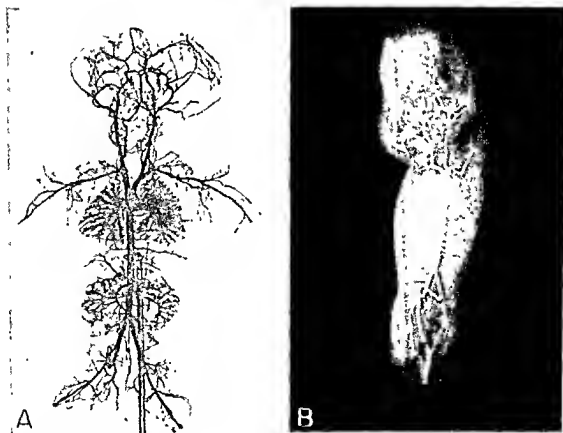


Figure II-40. A. The arterial system of a human fetus at about the transition from the 6th to the 7th month of gestation. (Photograph of a specimen prepared by Dr. O. Sankott of Vienna by postmortem injection followed by corrosion.) B. Angiocardiogram from a living human fetus early in the 4th month of gestation. (Photograph generously loaned by Dr. Carl Wegelius and Dr. John Lind of Stockholm, Sweden.) In this case the injection of the thorotrast was "retrograde;" that is, it was made into the umbilical arteries against the normal direction of blood flow. Therefore, the pressure under which it reached the orifices of the renal and the pulmonary arteries was definitely above normal.

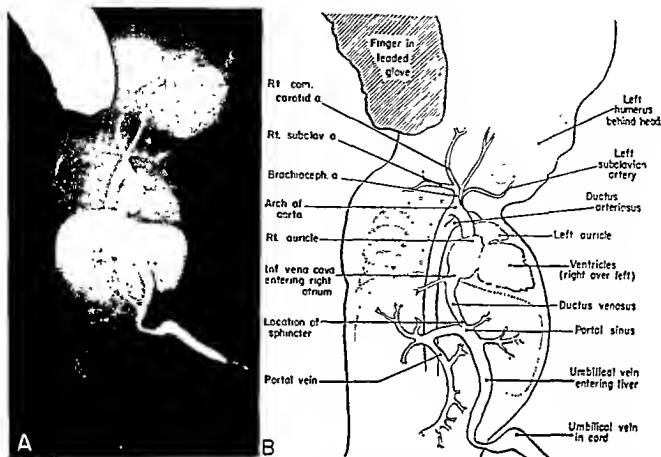


Figure 11-41. A Right anterior oblique angiocardiogram from human fetus of the fourth month. (Photograph generously loaned by Dr. Carl Wegelius and Dr. John Lind of Stockholm, Sweden.) The injection of the thorotrast was made through the umbilical vein in such a manner as to disturb the normal course of the circulation as little as possible. The particular exposure here reproduced was made when the ventricles had started to pump the blood out through the aorta and the pulmonary trunk. Note that, although the ductus arteriosus is clearly demonstrated, the area occupied by the right lung, well exposed in this view, as yet shows no readily visible filling of the pulmonary arteries. B. Diagrammatic key to aid in the interpretation of the angiocardiogram.

mechanically changes conditions at the time of birth, there is, nevertheless, a similar restriction of blood flow prenatally and a similar postnatal increase. In the fetal kidneys, as in the lungs, retrograde injections under increased pressure result in prompt filling of good-sized vessels. These findings suggest the probable importance of vasomotor control in organs not working at high functional levels during intrauterine life. The circumnata changes in renal circulation are less dramatic than those in the lungs but they are highly significant. One only needs to imagine what would happen if the fetus voided urine into its amniotic cavity prenatally at the same rate the newborn infant excretes it postnatally. Fragmentary observations seem to indicate

that the enteric vessels, like the pulmonary and the renal vessels, carry a restricted flow in the fetus.

Although, as we have seen, this recent work with living material has forced revision of some impressions based on structural conditions, it has given striking confirmation to other inferences. Synthesizing the most significant of the information from the study of structural conditions with the newer experimental evidence, the course followed by the blood in passing through the fetal heart may be summarized somewhat as follows. The inferior caval entrance is so directed with reference to the foramen ovale that a considerable portion of its stream passes directly into the left atrium (Figures 11-19, 11-20, 11-39,

and II-43). The resultant simultaneous filling of the two atria is clearly shown by angiocardigrams (Figure II-42).

It seems probable that the blood entering the heart from the inferior vena cava must show considerable fluctuation in its oxygen concentration. A definite sphincter-action has been seen at the origin of the ductus venosus from the umbilical vein (Figure II-39). When the sphincter is constricted, direct flow from the umbilical vein into the ductus venosus is retarded and relatively more blood is forced to reach the inferior vena cava by way of the tortuous route through the hepatic sinusoids. In this passage it must give up considerable oxygen along with food materials. When the sphincter is relaxed, blood can pass freely through the ductus venosus. Under these

conditions it would give up relatively little oxygen in its rapid passage from placenta to heart. There is also another modifying factor. The periodic uterine contractions must alter the rate at which blood passes through the placenta. When the flow from the placenta through the umbilical vein and the ductus venosus is strong, it may temporarily hold back any blood from entering the circuit by way of either the portal vein or the inferior caval tributaries (Figure II-39). For a time, under these conditions, the left atrium would be charged almost completely with fully oxygenated blood (Whitehead, 1942). Injection experiments which involve increasing pressure in, or adding volume by way of, the umbilical vein create a similar situation. Such condition in the living fetus, however, would be

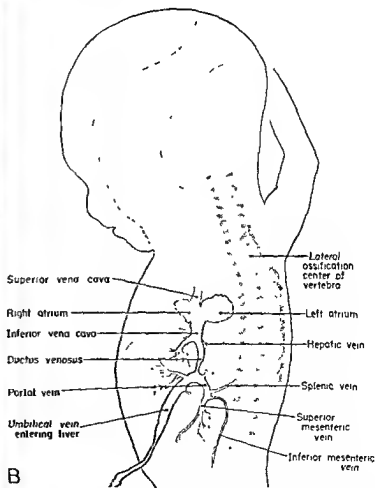


Figure II-42. A. Left anterior oblique angiocardigram showing contrast medium entering the atria following an injection through the umbilical vein. (Photograph generously loaned by Dr. Carl Wegelius and Dr. John Lind of Stockholm, Sweden.) Note especially the simultaneous filling of the two atria, indicating the way the blood entering from the inferior vena cava is divided at the lumens of the foramen ovale. (See arrow in Figure II-20.) B. Diagrammatic key to aid in the interpretation of the angiocardigram.

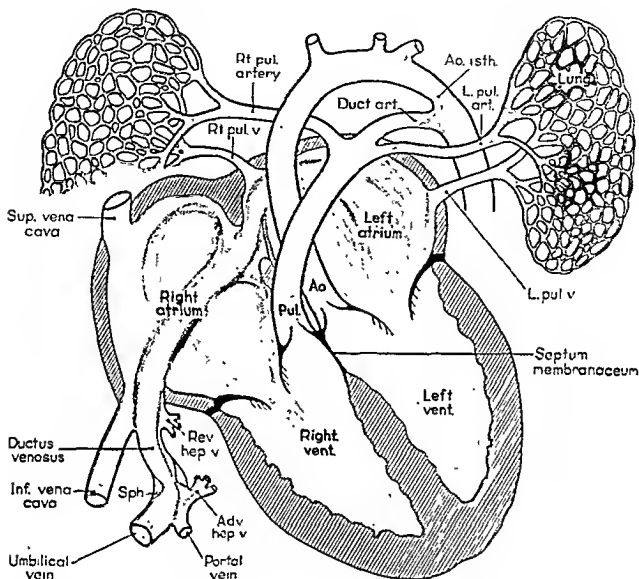


Figure 11-43. Schematic diagram showing course of blood through fetal heart just prior to birth. The colors symbolize relative degree of oxygen saturation.

Abbreviations: Ao. isth., aortic isthmus; Adv. hep. v., adherent hepatic vein; Duct. art., ductus arteriosus; Rev. hep. v., revent hepatic vein; Spl., splenic. When this sphincter is closed, blood from the umbilical vein is forced to pass through the sinusoidal channels of the liver, rather than taking the direct route through the ductus venosus.

but temporary and would be counterbalanced by periods when the portal and systemic veins poured enough blood into the common channels to load the heart for a time with mixed or oxygen-depleted blood. The important thing physiologically is the maintenance of the average oxygen concentrations of the blood at adequate levels, rather than the fluctuations.

It is also significant that careful measurements have shown that the interatrial com-

munication in the heart of the fetus at term is considerably smaller than the inferior caval inlet (Figure 11-45). This would mean that the portion of the inferior caval stream which could not pass across to the left atrium would eddy back and mix with the rest of the blood in the right atrium (Patten, Sommerfield and Paff, 1929). The work of Barcroft and his collaborators and that of Wegelius and Lind, referred to above, has given experimental confirmation of this conclusion.

From the standpoint of smooth postnatal circulatory readjustments, the larger the pulmonary return becomes during fetal life, the less will be the balancing transatrial flow, and the less will be the change entailed by the assumption of lung-breathing. Very early in development, before the lungs have been formed, the pulmonary return is negligible and the flow from the right atrium through the interatrial ostium primum constitutes virtually the entire intake of the left atrium. After the ostium primum is closed and while the lungs are but little developed, flow through the interatrial ostium secundum must still be the major part of the blood entering the left atrium. During the latter part of fetal

life the foramen ovale in septum secundum becomes the transeptal route. As the lungs grow and the pulmonary circulation increases in volume, a progressively smaller proportion of the left atrial intake comes by way of the foramen ovale and a progressively larger amount is derived from the vessels of the growing lungs.

The balanced atrial intake thus maintained implies a balanced ventricular intake, and this in turn implies a balanced ventricular output. We have seen, not in the heart itself but in the closely associated great vessels, a mechanism which affords an adequate outlet from the right ventricle during the period when the pulmonary circuit is developing.

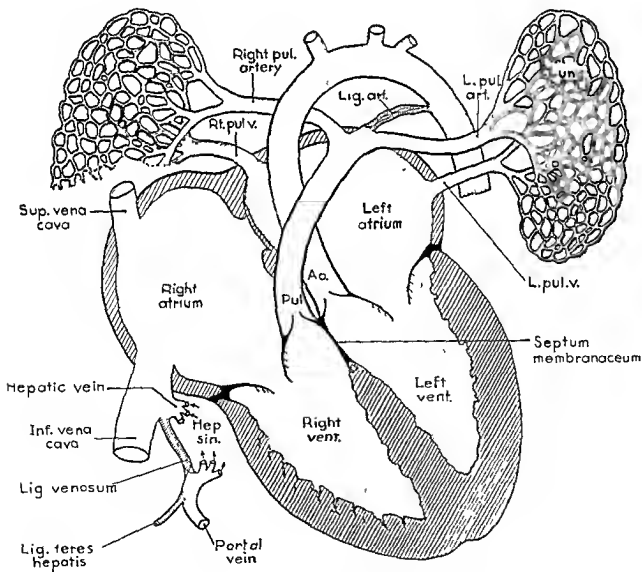


Figure II-44. Diagram showing schematically the changes occurring in circulation at time of birth.

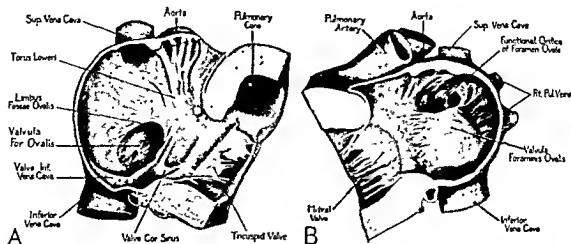


Figure II-45. Interior views of scale model of the human heart at term. A. Right atrial aspect showing foramen ovale. B. Left atrial aspect showing outlet (functional orifice) of foramen ovale into left atrium. Note that the valvula foraminis ovalis is bound sufficiently close to the septum so that the functional orifice is considerably smaller than the oval opening in septum secundum. (After Patten, Sommerfield and Pass, *Anat. Rec.*, Vol. 44, 1929.)

When the pulmonary arteries are formed from the sixth pair of aortic arches, the right sixth arch soon loses its original connection with the dorsal aorta. On the left, however, a portion of the sixth arch persists as a large vessel connecting the pulmonary artery with the dorsal aorta (Figures II-9, II-10 and II-39). This vessel, already familiar to us as the ductus arteriosus, remains open throughout fetal life and acts as a shunt, carrying over to the aorta whatever excess of blood the vascular bed of the lungs at any particular phase of its development is not prepared to receive from the right ventricle. As has already been pointed out, the ductus arteriosus can be called the "exercising channel" of the right ventricle, because it makes it possible for the right ventricle to carry its full share of work throughout development and thus be prepared for pumping all the blood through the lungs at the time of birth.

Postnatal Circulatory Changes. The two most obvious changes which occur in the circulation at the time of birth are the abrupt cutting off of the placental blood stream and the immediate assumption by the pulmonary circulation of the function of oxygenating blood (Figure II-44). One of the most impressive things in embryology is the perfect preparedness for this event which has been built into the very architecture of the circulatory system during its development. The shunt

at the ductus arteriosus which has been one of the factors in balancing ventricular loads throughout development, and the valvular mechanism at the foramen ovale, which has at the same time been balancing atrial intakes, are perfectly adapted to maintain an effectively balanced pumping load within the heart, in spite of the changes in peripheral blood routes which occur at the time of birth.

The opening of the vascular bed in the lungs is the event of primary functional interest. There are various factors involved, most of which have been suggested in one way or another in the discussion of prenatal conditions. With the beginning of respiration, the release of compression and the massaging effect of respiratory movements facilitate the passage of blood through the pulmonary capillary bed. In addition to these changes, according to Reynolds' concept, the straightening of spiral arterioles when the lungs are inflated would account for freer flow into the capillary bed. Although the evidence is still fragmentary, it seems probable that vasomotor changes also are involved. Edwards (1957) has called attention to the conspicuously heavy muscle coat of the pulmonary arterioles in fetal lungs. If vasoconstriction of these vessels is, as suspected, a factor in restricting prenatal blood flow through the lungs, their dilation following birth might

well be involved in bringing the pulmonary circulation into full activity. Further work is necessary before we can be certain of the relative importance of the various factors involved, but there can be no doubt regarding

the primary significance of lowered peripheral resistance in the pulmonary circulation.

The postnatal changes in flow through the ductus arteriosus are obviously correlated with the changes in the peripheral circulation

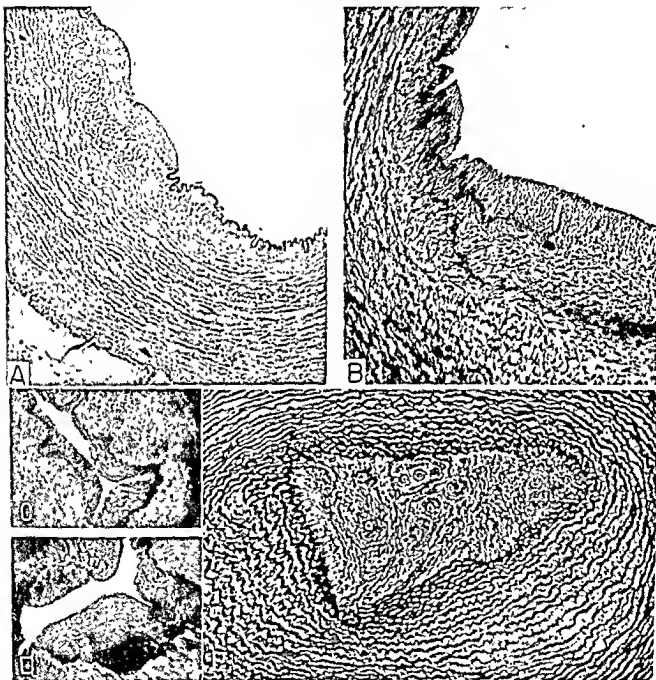


Figure II-46. Histologic changes involved in the closure of the ductus arteriosus. A. Photomicrograph of wall of ductus from a fetus stillborn at term, specifically stained for elastin. Note the typical appearance of the internal elastic lamina in the lower right part of the wall and, upper left, the pad-like thickening of the intima. In this locally thickened region the elastic lamina is replaced by exceedingly fine and closely woven fibers. B. A similar intimal pad from the ductus arteriosus of a 3-day infant. (Preparation, courtesy of Dr. Jesse E. Edwards.) C. Ductus of a 21-day infant, in low magnification, showing the growth and coalescence of the intimal pads. D. Similar section at 30 days. The progress of occlusion is clearly indicated by markedly increased thickness of intima. E. Weigert-picrofuchsin preparation of the recently closed ductus of a pig. This specifically stained preparation shows the important part played by elastic tissue in the intimal thickening which progressively occludes the ductus. (Parts C-D from Schaeffer, in Curtis, *Obstetrics and Gynecology*, 1933, courtesy of W. B. Saunders Company.)

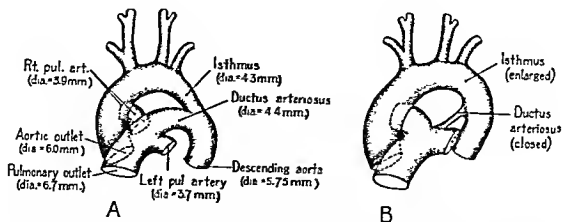


Figure 11-47. Diagrams showing characteristic postnatal changes in isthmus region of aortic arch. A. Fetal condition at full term. The vessel diameters are averages from the measurements of the internal diameters in 30 hearts. B. Typical configuration three to four months after birth. Note enlargement of isthmus portion of the aortic arch which accompanies reduction of ductus arteriosus. (Slightly modified from Patten, *Am. Heart J.*, Vol. 6, 1930.)

through the lungs. The problem of particular interest here is whether the closure of the ductus arteriosus forces blood through the lungs, or lowering of peripheral resistance in the pulmonary circuit causes the shunt through the ductus arteriosus to be abandoned.

It has long been known that the lumen of the ductus arteriosus is gradually occluded postnatally by an overgrowth of its intimal tissue (Schlaeffer, 1914; Scammon and Norris, 1918; Melka, 1926; Jager and Wollenman, 1942). This process in the wall of the ductus is as characteristic and regular a feature of the development of the circulatory system as the formation of the cardiac septa. Its earliest phases begin to be recognizable in the fetus as the time of birth approaches, and postnatally the process continues at an accelerated rate, to terminate in complete anatomic occlusion of the lumen of the ductus about six to eight weeks after birth. Barclay, Franklin and Prichard (1914) have conducted a series of experiments on animals delivered by cesarean section, which indicate that the ductus arteriosus closes functionally far sooner than it does anatomically. Following birth there appears to be a contraction of the circularly disposed smooth muscle in its wall, promptly reducing the flow of blood through the ductus. Such a reduction in the shunt from the pulmonary circuit to the aorta, acting along

with the newly assumed respiratory activity of the lungs themselves, would aid in raising the pulmonary circulation to full functional level. At the same time, the functional closure of the ductus by muscular contraction would pave the way for the ultimate anatomic obliteration of its lumen by overgrowth of intimal connective tissue (Figure 11-46). This concept of the immediate closure of the ductus by muscular action is so appealing on theoretical grounds that a little extra caution in evaluating the evidence is indicated. It should be borne in mind that an initial tendency on the part of the circular smooth muscle of the ductus to contract does not necessarily imply a contraction sufficiently strong and steadily maintained to shut off all blood flow during the six to eight weeks required for morphologic closure (Kennedy and Clark, 1911). Furthermore, we should remember that the lowering of peripheral resistance in the small vessels of the lungs may well lessen the force of the shunt through the ductus arteriosus to a point where it would take little more than the natural elasticity of the vessel walls to bring about apparent closure. Finally, the dramatic quality of an immediate functional closure, by whatever mechanism it is effected, should not cause us to forget the importance of the slower but more positive structural closure.

The closure of the ductus arteriosus entails

a gradual, although none the less striking, change in the configuration of the aortic arch (Patten, 1930; Noback and Rehman, 1941). Before birth there is a definitely narrowed portion of the arch between the point where the left subclavian is given off and the point of entrance of the ductus arteriosus. This narrowed region is called the *isthmus* (Figure

II-47A). After the ductus arteriosus has been closed, all the blood entering the descending aorta must traverse the aortic arch and, as a result, the isthmus is slowly enlarged. It is usually three to four months after birth before all trace of the narrowing which was so characteristic of the arch of the fetal aorta has entirely disappeared (Figure II-47B).

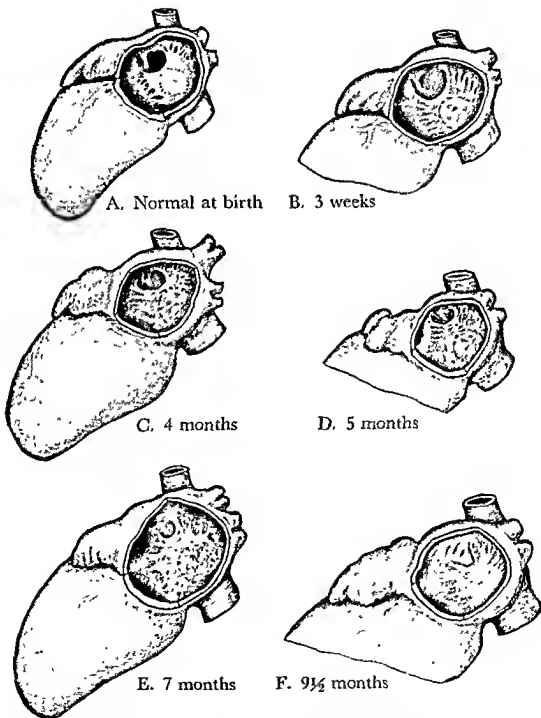


Figure II-48. Drawings of hearts with left atrium opened to show gross changes in valvula during period of closure of foramen ovale. Compare with Figure II-49, showing the microscopic changes. (From Patten, *Am. J. Anat.*, Vol. 48, 1931.)

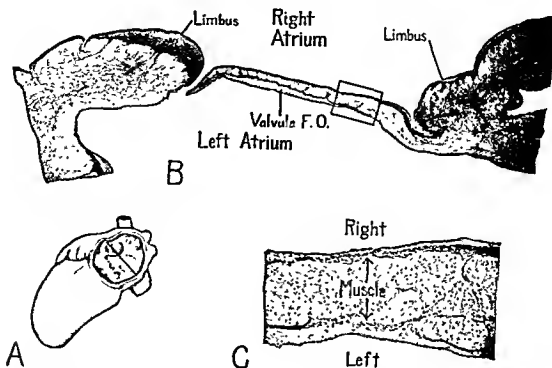


Figure 11-49. Structure and relations of valvula foraminis ovalis at time of birth. A. Orienting-sketch with left atrium opened. Heavy black line indicates location of section shown in B. B. Photomicrograph of section passing through interatrial septum at foramen ovale. C. More highly magnified photomicrograph of section through valvula at point indicated by rectangle on B (From Patten, *Am. J. Anat.*, Vol. 48, 1931.)

The results of increased pulmonary circulation with the concomitant increase in the direct intake of the left atrium are manifested secondarily at the foramen ovale. Following birth, as the pulmonary return increases, compensatory blood flow from the right atrium to the left decreases correspondingly, and soon ceases altogether. This is indicated anatomically by a progressive reduction in the looseness of the valvula foraminis ovalis and the consequent diminution of the interatrial communication to a progressively narrower slit between the valvula and the septum (Figure 11-48). When equalization of atrial intakes has occurred, the compensating one-way valve at the foramen ovale falls into disuse. Although, for several months after birth, a probe can still be passed freely behind the valvula, the foramen ovale may be regarded as functionally closed when this new intracardiac balance has been attained.

Then follows a period of six to eight months in which the connective tissue of the valvula increases from 600 to 700 per cent (Figure 11-50). This second phase in the closure of

the foramen ovale with its characteristic histologic alteration is essentially the conversion of an originally movable, flap-like valve into a fixed septal structure (Patten, 1931). Finally, coming leisurely in the wake of functional abandonment and as a culmination of the period of connective-tissue proliferation, is the adhesion of the valvula to become an integral part of the interatrial septum. There is great variability in the age at which this final step in the closure of the foramen ovale occurs. A usual range, rather than a specific time of final anatomic closure, is all that can be stated. Substantiated instances of fibrous adhesion of the valvula to the septum becoming complete under three months are exceedingly rare. The usual time of complete anatomic closure appears to be not earlier than the last third of the first year after birth, and frequently it is much later.

In 20 to 25 per cent of persons the fibrous adhesion of the valvula to the septum is never entirely completed (Figure 11-51). Provided the valvula simply overlaps the foramen ovale, such failures of complete adhesion appear to

be no functional handicap to otherwise normal persons. The condition is best described as *probe-patency* (Patten, 1931, p. 40) in distinction to *open foramen ovale with incompetent valve* (cf. Figures II-51 and II-52). Because of the frequency with which they occur,

probe-patencies may well be regarded as variations of the normal rather than as abnormalities. Such an attitude, however, must be tempered by the realization that in the event of disturbances in the pulmonary circuit sufficiently severe to unbalance intra-

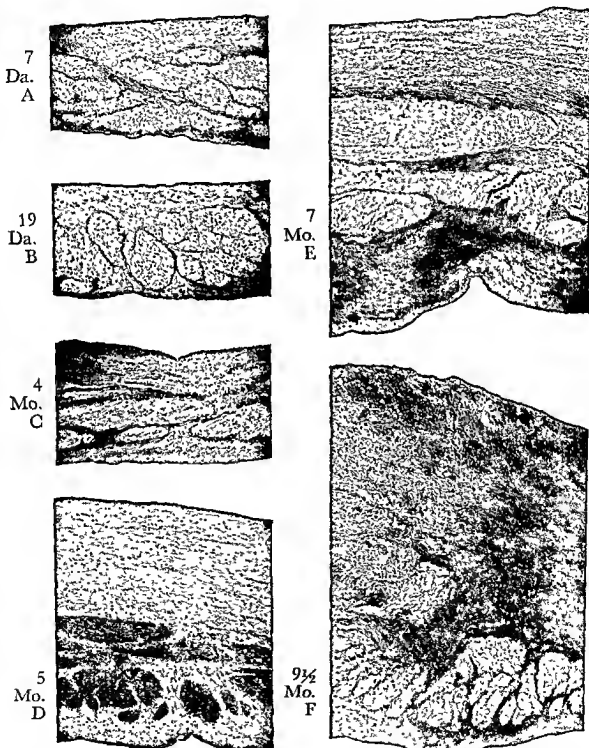


Figure II-50. Histologic changes in valvula foraminis ovalis following birth. (Photomicrographs, X 80.) For comparable area, at birth, see Figure II-49. (From Patten, *Am. J. Anat.*, Vol. 48, 1931.)

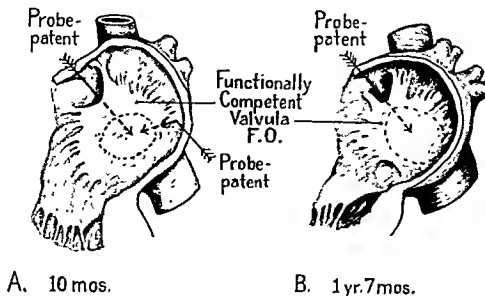


Figure 11-51. Examples of heart showing the foramen ovale guarded by a valvula ample in its overlap, but incompletely fused to the septum. Such hearts show what may be designated as adequate functional closure with a persistent probe-patency. Probe-patencies of this type are apparently no functional handicap to an otherwise normal person and persist in from 20 to 25 per cent of all adults (From Patten, *Am. J. Anat.*, Vol. 48, 1931.)

atrial pressures, an area of incomplete adhesion may again become a path for trans-septal flow (see Chapter VI, page 282).

Quite different from cases of nonadherence of the valvula with mere probe-patency are those in which the valvula is actually incompetent to close the foramen ovale (Figure 11-52). Such a condition may be caused by abnormally extensive resorption of septum primum in connection with the formation of ostium secundum, or by insufficient growth of septum secundum leaving an abnormally large foramen ovale, or by a combination of both of these conditions (Patten, 1938). The functional implications of such interatrial defects will be discussed in Chapter VI.

Even in the cases in which complete fibrous adhesion has occurred, the fetal valvular mechanism at the foramen ovale leaves its imprint on the anatomy of the adult heart. The sharply marked margin of the fossa ovalis records the former boundaries of the foramen ovale in septum secundum (Figure 11-53). The thin interatrial wall of the fossa itself is septum primum, closing the fetal opening. When one inserts a probe under the margin of the fossa ovalis to see whether or not it can be pushed all the way into the left atrium,

one is but prying at the seal placed on the foramen ovale following birth.

The foregoing discussion of the postnatal occurrences at the ductus arteriosus and at the foramen ovale was predicated on the normal development of the lungs and their vessels. If there is any failure in the pulmonary system, the story is different. A blood stream, like any other fluid current, is bound to seek the path of least resistance. Normally, when respiration in the lungs commences, the peripheral resistance of the pulmonary circulation is sufficiently reduced so that the blood pumped over the pulmonary trunk all goes to the lungs rather than forcing its way over the ductus arteriosus against the now higher pressure of the aortic stream. If, through any deficiency in the development of the lungs themselves, or of their vessels, undue resistance to the free passage of blood exists, the pulmonary artery will continue to shunt a portion of its blood stream over the ductus arteriosus to the aorta just as it did before birth. That this happens but rarely is perhaps the most remarkable fact about the entire series of circulatory changes which take place at birth; for there is no way this peripheral part of the pulmonary circulation can be tested

under functional conditions while the fetus remains *in utero*. Yet, the instances in which it fails the test of immediate functional adequacy at the time of birth are exceedingly few.

In the exceptional cases in which the pulmonary circulation does not at once begin to function properly, the entire balance within the heart is upset. The blood which fails to enter the lungs goes through the ductus arteriosus into the aorta and is returned by the systemic veins to the right atrium. The same process reduces the amount of blood which reaches the left atrium by way of the pulmonary veins. This causes a marked inequality in the volume of blood entering the two atria and a resultant inequality of the blood pressure on opposite sides of the interatrial septum. Consequently, unoxygenated blood passes through the foramen ovale from right to left and the infant is cyanotic. The primary cause of the difficulty is not, as is so often misstated, the "failure of the foramen ovale to close at birth." Its structural closure is always a gradual process. It is open throughout fetal life or the embryo would not have sufficient left ventricular development to carry the systemic circulation, and it normally remains structurally unclosed for most of the first postnatal year. What does occur in these cases is failure to establish balanced pressure conditions which effect prompt functional closure, and at the same time facilitate the gradual structural closure of the foramen ovale.

With birth and the interruption of the placental circuit, there follows the gradual fibrous involution of the umbilical vein and the umbilical arteries. The flow of blood in these vessels, of course, ceases immediately with the ligation of the umbilical cord, but obliteration of the lumen is likely to take from three to five weeks, and isolated portions of these vessels may retain a vestigial lumen for much longer. Ultimately these vessels are reduced to fibrous cords. The old course of the umbilical vein is represented in the adult by the ligamentum teres from the umbilicus to the liver, and within the substance of the liver by the ligamentum venosus. The proximal portions of the umbilical arteries are retained

in reduced relative size as the hypogastrics. The fibrous cords extending from these arteries on either side of the urachus toward the umbilicus are the remains of the more distal portions of the old umbilical arteries, known in the adult as the "obliterated branches" of the hypogastric arteries.

Slowest of the postnatal changes to be completed is the muscular development of the left ventricle. At the close of fetal life the right and left ventricular walls are of approximately equal thickness. Actually the right ventricular myocardium outweighs the left slightly, the ratio of their weights being approximately 8 to 7 (Patten, 1930). This is consonant with the slightly greater capacity of the right ventricle and the greater size of the pulmonary outlet as compared with the aortic outlet. Physiologically, these structural conditions are reflected by the right preponderance exhibited by neonatal electrocardiograms and a pulmonary pressure enough higher than the aortic to maintain blood flow in the ductus arteriosus toward the aorta during fetal life. Postnatally, with the structural closure of the ductus arteriosus securely accomplished, the pressure conditions change. The left ventricle must thereafter carry the full load of the longer systemic circuit with no assistance from the right. In response to this added work, the thickness of the left ventricular wall gradually increases and aortic pressure rises. Gross (1921) believed that it took three to four years after birth before the left ventricular wall acquired its full adult degree of preponderance. More recently, Keen (1935) has presented data indicating that the greater part of this change is accomplished within the first six months after birth.

Much yet remains to be learned as to the more precise physiology of the fetal circulation and as to the interaction of various factors during the transition from intra-uterine to postnatal conditions. Nevertheless, with our present knowledge it is quite apparent that the changes in the circulation which occur following birth involve no revolutionary disturbances of the load carried by different parts of the heart. The compensatory mechanisms at the foramen ovale and the ductus

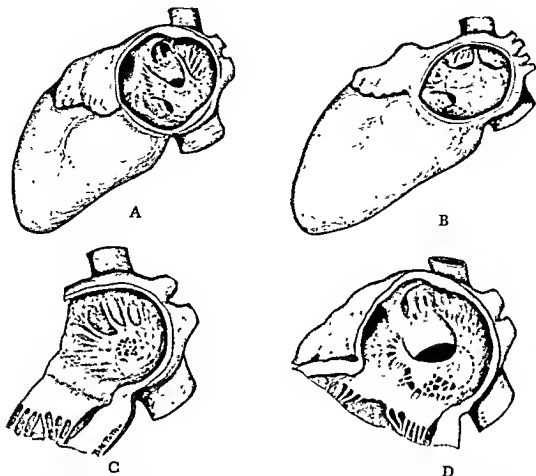


Figure 11-52. Various types of defects in valvular mechanism of foramen ovale which prevent effective closure. A Defect caused by overresorption of septum primum. (Stillborn, autopsy 176,204, *Path Inst.*, Vienna.) B Defect caused by underdevelopment of septum secundum leaving an abnormally large foramen ovale. (Female, lived 16 hours, autopsy 176,346, *Path Inst.*, Vienna.) C Perforated valvula, resorption in abnormal locations. (Male, age three months, autopsy 176,312, *Path Inst.*, Vienna.) D Extensive valvular defect involving a combination of all three of the above factors. (Specimen 4093, Rokitsky Museum, Vienna, from forensic autopsy of child aged about five months.) (From Patten, *Am. J. Path.*, Vol. 14, 1938.)

arteriosus which have been functioning all during fetal life are entirely competent to effect the establishing of the final postnatal circulation with a minimum of functional disturbance. It is still true that as individuals we crowd into a few crucial moments the change from water-living to air-living that in phylogeny must have been spread over eons

of transitional amphibious existence. But as we learn more about this change in manner of living, it becomes apparent that we should marvel more at the completeness and the perfection of the preparations for its smooth accomplishment, and dwell less on the old theme of the revolutionary character of the changes involved.

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The Structure of the Adult Heart

ALEXANDER BARRY AND BRADLEY M. PATTEN

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THE HEART AS A WHOLE

Shape and Relations. The adult heart is a roughly conical, hollow, muscular organ with walls consisting of three layers: endocardium, myocardium, and epicardium (visceral pericardium). The epicardium is a serous membrane, continuous with the parietal pericardium which lines the pericardial cavity. The base of the heart is poorly circumscribed but corresponds in a general way with the area occupied by the great vessels entering and leaving the heart, together with that portion of the heart wall which lies between them. The heart is held in position within the pericardial cavity by these great vessels and the visceral pericardium (epicardium), which is reflected at their roots to become continuous with the parietal pericardium. Thus, the heart is not rigidly fixed within the pericardial cavity; during its contraction both its base and

its apex undergo changes in position, and the heart as a whole is freely movable within the pericardial cavity.

The Chambers of the Heart. The heart is divided into four chambers: two thin-walled atria which serve as the intake chambers, and two heavy-walled ventricles the contractions of which carry out the effective pumping action of the heart. The interior of the heart is divided into right and left sides by a partition passing from base to apex. The cavity of each atrium opens into the cavity of its corresponding ventricle by way of an atrioventricular ostium. The right atrium receives blood from the superior and inferior venae cavae and the coronary sinus, and passes it on to the right ventricle which pumps it into the pulmonary trunk. The left atrium receives blood from the four pulmonary veins, and passes it on

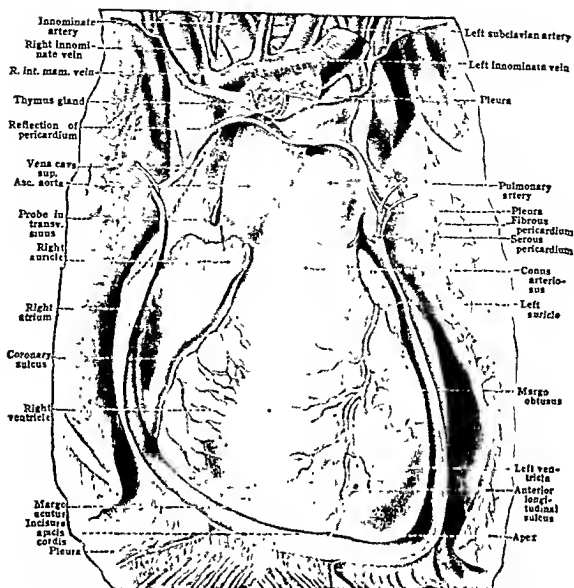


Figure III-1. Ventral view of heart *in situ* with the pericardial sac opened. (After a dissection by R. T. Blount, drawn by Jean Hirsch, from Morris' *Human Anatomy*, courtesy of The Hinkston Company, Philadelphia.)

to the left ventricle which pumps it into the ascending aorta.

Terminology. In descriptions of the anatomy of the heart, confusion often arises because of the terminology used in describing relationships. Such terms as "in front of," "behind," "above," "below" are not sufficiently unequivocal for anatomic description. The terms "anterior" and "posterior" may be interpreted differently by different readers. In the following account the major axes will be described as *cephalic* and *caudal*, *dorsal* and *ventral*, and *right* and *left*. Although these terms lead to phrases that at times seem awkward, nevertheless they avoid ambiguity, and

will be employed except where their use does violence to such venerable and deeply rooted terms as "anterior papillary muscle," or "anterior and posterior semilunar valves." In such instances consistency may well be sacrificed to tradition.

Orientation. Although the heart is commonly described as consisting of right and left halves, its longitudinal axis does not lie in the sagittal plane of the body. The apex of the heart points ventrally, to the left, and caudally. Its longitudinal axis forms an angle of approximately 40° with the horizontal, and is inclined to the right to form about the same angle with the sagittal plane. Therefore, the

right and left atria do not lie cephalic to the corresponding ventricles but rather dorsal to, and to the right of them.

Size and Weight. In the average adult the heart measures about 12.5 cm. (5 in.) from base to apex, and 8.7 cm. (3½ in.) in its broadest dimension. In a man its weight is about 312 grams (11 ounces), and in a woman, about 225 grams (8 ounces). The weight of the heart makes up about 0.4 to 0.5 per cent of the total body weight of the

average adult. At birth it averages about 0.7 per cent of the total body weight. In emaciated persons the heart weighs relatively more, and in the obese, relatively less. The volume of the heart may be estimated in a living person by means of its x-ray silhouette.*

* If the area of this silhouette be determined in square centimeters, and appropriate correction be made for divergence of the rays, then the volume of the heart, in cubic centimeters, will be $0.53A^{3/2}$, when A is the area of the heart shadow, and the weight of the heart will be $1/20 A^{3/2}$ (0.0055) (Bardeen, 1918).

EXTERNAL ASPECT OF THE HEART

Ventricular Portion. The apex of the heart is formed by the left ventricle. The average position of the apex border in the erect individual is at the level of the sixth rib. This position in a series of 192 young adult men has been found to vary between the fifth rib and the sixth interspace (Woodburne and Whitaker, 1943). In the supine position and in measurements in cadavers, this location, like other similar relationships with skeletal landmarks, will tend to be half an interspace

higher. In hearts that have been hardened by fixation within the pericardial cavity, the conical regularity of the ventricular portion is disturbed by a well-marked triangular facet caused by contact with the diaphragm. This area of contact, the so-called diaphragmatic surface, of necessity has a contour conforming to that of the upper surface of the diaphragm, and so faces caudally and slightly dorsally. Its ventral margin is marked by an abruptly curved edge running from the apex



Figure III-2. Teleroentgenogram of a cadaver, showing the relations of the heart, diaphragm, great vessels and ventral thoracic cage. (After LeWald, from Morris' *Human Anatomy*, courtesy of The Blakiston Company, Philadelphia.) The atrioventricular, aortic and pulmonary ostia have been fitted with wire rings to show their respective positions. In such embalmed preparations, these positions are about half an interspace higher than they are in the living erect subject.

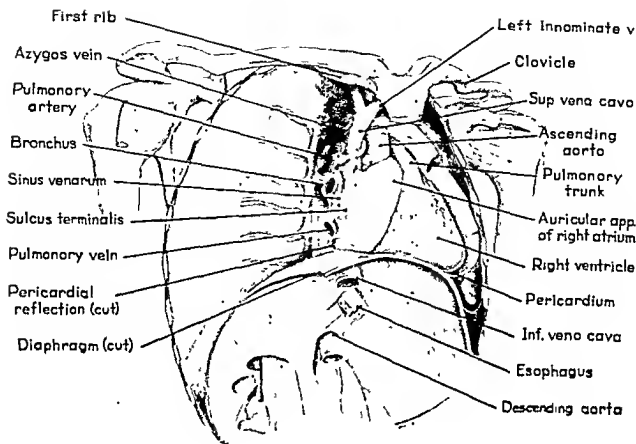


Figure III-3 Right anterior oblique view of the heart *in situ*. The adjacent viscera have been removed and the pericardial sac has been opened.

to the right, as far as the right atrium. This margin is called the *margo acutus* (Figure III-1), and marks the transition between the diaphragmatic surface of the heart and its *sternocostal* surface, which faces the sternum and costal cartilages. The dorsal edge of the diaphragmatic surface is more rounded than the *margo acutus*, and sweeps cephalically to form the dorsal side of the heart. The left surface of the ventricular portion of the heart is called the *margo obtusus*. It forms the rounded left side of the left ventricle, and extends from the ventricular apex to the root of the pulmonary trunk. The *margo obtusus* passes gradually over into the sternocostal surface of the heart.

The *interventricular sulcus* is a shallow groove which indicates, on the surface of the heart, the location of the internal partition separating the two ventricles. In it lie coro-

nary blood vessels, nerves, and a variable amount of fat. The part of this sulcus seen on the sternocostal surface is the *anterior longitudinal sulcus* (Figure III-1) which originates at the left of the root of the pulmonary trunk, runs obliquely over the upper part of the *margo obtusus*, and courses nearly vertically down over the sternocostal surface. As it crosses the *margo acutus* it forms a slight notch, the *incisura apicis cordis*, and is continued as the *posterior longitudinal sulcus* on the diaphragmatic surface.

The diaphragmatic surface is constituted about equally by the right and left ventricles, whereas the sternocostal surface is formed mainly by the right. The external line of demarcation between the atria and the ventricles is the *coronary sulcus*. On the diaphragmatic surface of the heart, this groove is occupied by the *coronary sinus*. It is well marked along

the lateral and ventral aspects of the heart where it contains coronary arteries and veins embedded in a considerable amount of fat

Atrial Portion. The atrial portion of the heart lies to the right of, dorsal, and slightly cephalic to the ventricular portion. On the dorsal surface of the heart the division into right and left atria is not clearly indicated except in distended hearts, in which it is marked by a groove connecting the left sides of the superior and inferior venae cavae. Ventrally the right and left auricular appendages of the atria protrude to bound a deep notch in which lie the ascending aorta and the pulmonary trunk. On the dorsal aspect of the right atrium a slight groove is seen connecting the right sides of the superior and inferior venae cavae. This is called the *sulcus terminalis* (Figures III-3 and III-16) and represents the lateral boundary of what was the right horn of the embryonic sinus venosus which has been partially incorporated into the dorsal wall of the right atrium of the adult heart, forming the so-called *sinus venarum* (Figures III-3 and III-5).

The *superior vena cava* enters the right atrium cephalically while the *inferior vena cava* enters it from its caudal aspect. The axes of these two great veins are nearly in line with each other and with the vertical axis of the body. The *coronary sinus* originates by confluence of venous tributaries below the left caudal pulmonary vein, and courses in the coronary sulcus caudally, dorsally, and to the right, to enter the right atrium slightly nearer the right atrioventricular ostium than the entrance of the inferior vena cava. The pulmonary veins course transversely and somewhat cephalically to enter the right and left sides of the left atrium (Figures III-5 and III-6).

Arterial Outlets of the Heart. Viewed in ventral aspect, the right ventricle can be seen to extend cephalically and slightly to the left, bounded by the anterior longitudinal sulcus and the coronary sulcus. At the level between the second and third costal cartilages on the left, the pulmonary cone of the right ventricle gives rise to the *pulmonary trunk* (Figure III-1). This vessel curves abruptly dorsally and, after a distance of about one and one-half

inches (4.3 cm.), bifurcates into right and left pulmonary arteries. The pulmonary trunk is commonly referred to in clinical literature as the "undivided portion of the pulmonary artery," a prolixity that has little to recommend it.

The left ventricle discharges into the ascending aorta slightly to the left of the midline, at about the level of the attachment of the third costal cartilage. The orifice of the aorta lies dorsal, caudal, and slightly to the right of the pulmonary trunk (Figure III-19). The aorta may be divided into three portions for descriptive purposes: (1) the ascending aorta, running cephalically and very slightly to the right; (2) the aortic arch, which swings dorsally and to the left, arching over the right pulmonary artery and the bifurcation of the pulmonary trunk; and (3) the descending aorta, which passes caudally and, in its thoracic extent, lies to the left of the midline. From the aortic arch arise the large arteries that supply blood to the upper part of the



Figure III-4. Right anterior oblique roentgenogram of the thoracic region of the adult, taken from essentially the same angle as the drawing in Figure III-3 (Courtesy of the Department of Roentgenology, University of Michigan)

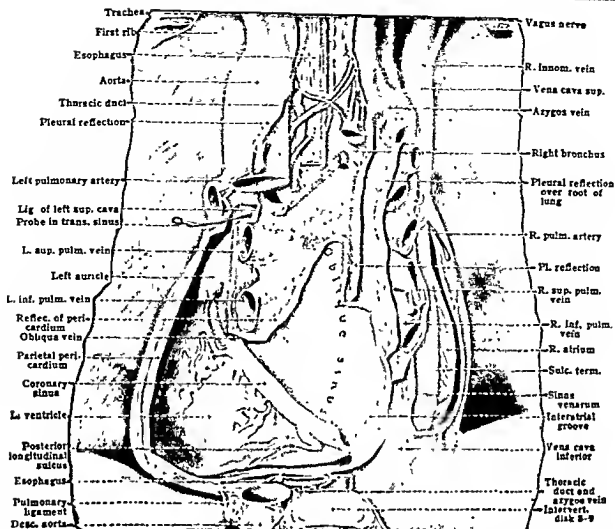


Figure III-5. Dorsal view of the heart *in situ*. The pericardial sac has been opened in such a manner that its reflections around the roots of the great vessels are emphasized. (After a dissection by H. F. Blount, drawn by Jean Hirsch. From Morris' *Human Anatomy* courtesy of The Blakiston Company, Philadelphia.)

body: the innominate, the left common carotid and the left subclavian. A ligament, about 3 to 5 mm. in diameter and from 8 to 15 mm. in length, connects the left pulmonary artery to the aortic arch. This is called the *ligamentum arteriosum* (Figure III-29). It is of importance as a landmark since it represents the fibrous remains of the ductus arteriosus of the fetus (Figures II-39 and II-47). It is attached to the cephalic aspect of the left pulmonary artery close to the bifurcation of the pulmonary trunk. It passes dor-

sally, slightly cephalically and to the left, to attach to the arch of the aorta on its caudal side slightly caudal to the origin of the left subclavian artery. One of the less uncommon anomalies of cardiac development is persistence of a patent ductus arteriosus. Such a retained fetal channel will have essentially the same relations as the *ligamentum arteriosum* of the normal adult, although there is a tendency for a patent ductus arteriosus to become shortened, a point of some surgical significance.

THE PERICARDIAL CAVITY

The heart, except for attachments at its venous and arterial ends, lies free within the pericardial cavity. This cavity is lined by a

serous membrane, the pericardium, consisting of a mesothelial layer and an underlying fibrous lamina. At the regions where the heart

is attached to the dorsal thoracic wall, the pericardium lining the wall of the pericardial cavity is reflected over the heart. In this position it is called the visceral pericardium or more commonly, by histologists, the epicardium. The positions of these lines of reflection are shown in Figures III-3, III-5 and III-6. Their embryologic derivation is indicated in Figures II-30 and II-31. There are essentially two regions of reflection, one surrounding the ascending aorta and the pulmonary trunk, and the other surrounding the great veins entering the atria. The pericardial reflection surrounding the venous inlets forms a mesentery-like membrane (mesocardium), which passes between the dorsal wall of the pericardial

cavity and the heart, and encloses the several inlets in a common investment. It has a cephalocaudal portion which extends between the caval inlets and includes the roots of the right pulmonary veins. It sweeps transversely from the right to the left superior pulmonary vein, and turns caudally to envelop the root of the left inferior pulmonary vein. This horse-shoe-shaped line of reflection partially isolates a portion of the pericardial cavity which is called the *oblique sinus* (Figures II-31E and III-6). The ring of pericardial reflection surrounding the ascending aorta and the pulmonary trunk is independent of the mesocardial complex surrounding the venous inlets. There is, therefore, a portion of the pericardial cavity

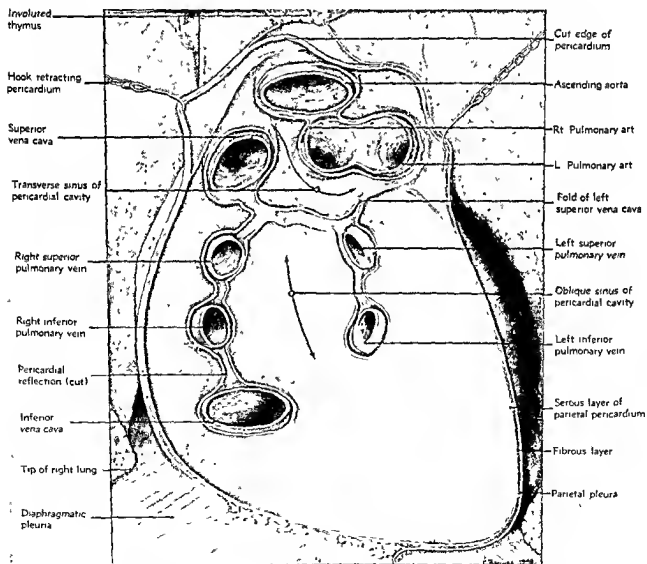


Figure III-6. Dorsal wall of the pericardial cavity. The heart has been removed in such a manner as to show the reflections of the pericardium around the roots of the great vessels. (See Figure II-33.)

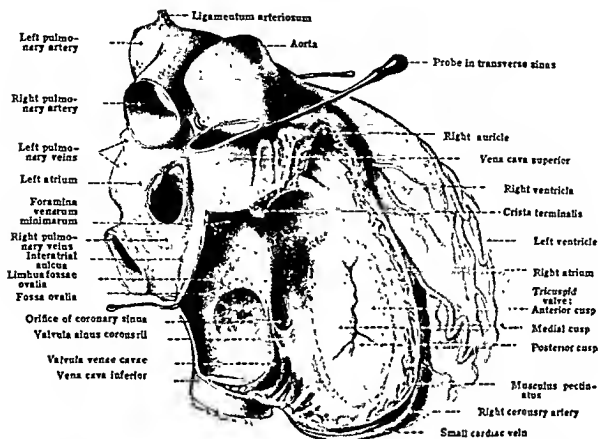


Figure III-7. Right anterior oblique view of the excised heart, with the right atrium opened to show its internal configuration. For orientation, compare with Figure III-3. (After a dissection by R. F. Blount. The original drawing by Jean Hirsch has been slightly modified. From Morris' *Human Anatomy*, courtesy of The Blakiston Company.)

running transversely across the midline immediately cephalic to the superior pulmonary veins and the superior vena cava. This is called the *transverse sinus* of the pericardial cavity. It represents in the adult the place where the embryonic dorsal mesocardium first broke through to make the right and left coelomic cavities confluent across the midline.

In some persons the left common cardinal vein (duct of Cuvier) may persist in the adult. This condition is usually spoken of as a double superior vena cava. Ordinarily in such cases there is present a left innominate vein of reduced size, and the left superior cava which enters by way of the coronary sinus is smaller than the right. Occasionally, by reason of a complete failure of the innominate to develop as a shunt from the left to the right anterior cardinal vein (Figure II-12), the two superior cavae may be of equal size, thus retaining the

primary bilateral symmetry of the embryonic venous system (Prows, 1943). More commonly the left common cardinal vein is reduced in size, and persists in the adult as a small vein coursing obliquely across the dorsal aspect of the left atrium, to the left of the left pulmonary veins (Marshall, 1830). This is called the *oblique vein of the left atrium* or *oblique vein of Marshall* (Figures II-30 and III-16). This vein may be continued cephalically as a small vein, or more commonly as a fibrous cord, to attach to the left highest intercostal vein. The parietal pericardium is usually pulled up into a fold by this vein or ligament to form the vestigial fold of the left superior vena cava (vestigial fold of Marshall). The vestigial fold of Marshall originates near the left entrance into the transverse sinus of the pericardial cavity, and can be traced cephalically and to the left (Figure

III-6). The attachment of this mesocardial fold to the dorsal wall of the pericardial cavity is not always found to the left of the left superior pulmonary vein as might be expected from the course of the oblique vein of Marshall, but may be secondarily displaced to the right so that it is situated within the transverse sinus itself.

THE INTERIOR OF THE HEART

The Interatrial Septum. The interior of the atrial portion of the heart is divided by the interatrial septum into right and left chambers. This septum is a composite structure, being derived from two independent septa of the embryonic atrium, neither one of which was formed as a complete partition in itself (Figures II-16, II-18, II-19 and II-20). The openings in the two embryonic septa do not normally coincide in position, so that when fusion of the septa is completed, usually during the first year of postnatal life, the impervious partition characteristic of the adult heart is formed. Traces of the two originally independent parts of the interatrial septum

The pericardial cavity of the normal adult contains about 25 or 30 ml. of pericardial fluid. This is a straw-colored serous fluid with essentially the composition of lymph. It serves to minimize friction between the visceral and parietal layers of the pericardium.

are, however, clearly recognizable in the adult. The crescentic margin of the old *valvula foraminis ovalis*, can be seen more or less firmly adherent to the left side of the septum (Figure III-10). The area cephalic to this margin represents the location of ostium II of interatrial septum primum of embryologic descriptions (Figure II-29). The main muscular part of the interatrial septum is derived from a septum (interatrial septum secundum) that forms somewhat later, immediately to the right of the septum primum. Septum secundum retains throughout fetal life an oval opening called the foramen ovale, the margin of which is seen on the right side of the adult

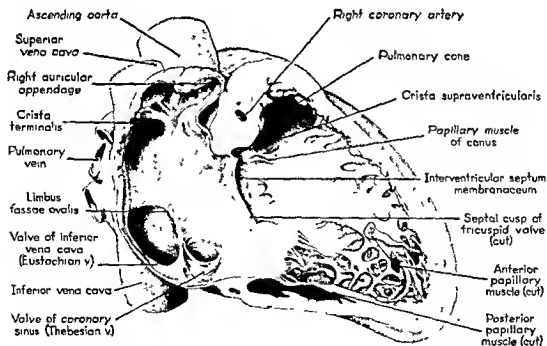


Figure III-8. Right side of the heart opened in a plane approximately parallel to the septa, to show the interior of the right atrium and the right ventricle. A segment of the septal leaflet of the tricuspid valve has been cut away to expose more fully the region of the membranous portion of the interventricular septum.

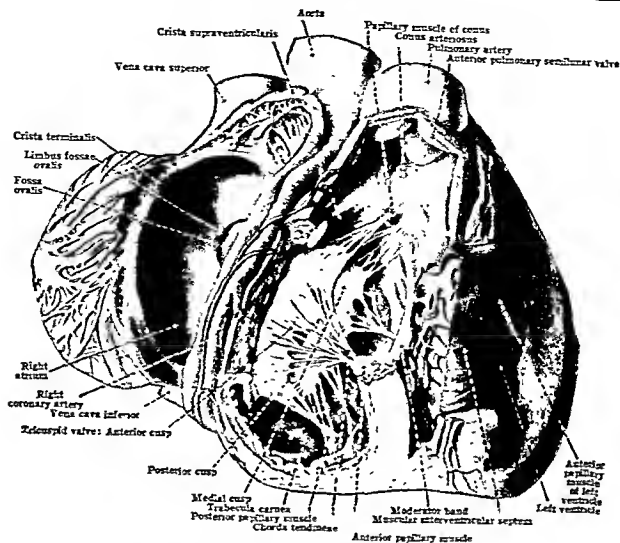


Figure III-9. Ventral view of the heart with the walls of the right atrium and ventricle opened to show their internal configuration. The dissection was planned to show the relations of an unusually well developed moderator band. In this heart the position of the foramen ovale is somewhat more cephalic than usual. (After a dissection by R. F. Blount, drawn by Jean Hirsch. From Morris' *Human Anatomy*, courtesy of The Blakiston Company, Philadelphia.)

interatrial septum as the *limbus fossae ovalis*. After the valve of the foramen ovale (*septum primum*) has fused to the left atrial side of the septum secundum, the foramen ovale becomes a more or less oval depression on the right side of the interatrial septum, called the *fossa ovalis* (Figure III-8). In some 20 to 25 per cent of adult hearts the fusion of the valve of the foramen ovale with the septum secundum is not complete. By following the direction of the inferior vena cava, a slender probe may be slipped under the *limbus fossae ovalis*, between the valve of the foramen ovale and the muscular portion of the septum, into the left atrium. This condition, characterized as "probe-patency" (Figure II-51), is discussed

in Chapter II. Such openings are vestiges of an important fetal blood route which is abandoned postnatally, after the lungs have become completely functional. Failure of complete fusion between the two parts of the embryonic interatrial septum with resulting probe-patency does not appear to be a handicap to an otherwise normal heart, and is of sufficient frequency to be regarded as a variant of the normal. Probe-patency should be sharply distinguished from a true valvular defect such as exists when the valve of the foramen ovale is incompetent to guard the foramen ovale.

The Right Atrium. The inferior vena cava passes through the diaphragm and enters the

caudal side of the right atrium (Figures III-3 and III-8). The inferior caval orifice is partially guarded along its ventral aspect by an incompetent valve flap of variable fullness, the *valve of the inferior vena cava* (eustachian valve). Dorso-caudally on the wall of the right atrium, between the atrioventricular orifice and the fossa ovalis, is located the opening of the coronary sinus, guarded by the *valve of the coronary sinus* (thebesian valve). Leading from the right atrium ventrally, slightly caudally, and to the left is the right atrioventricular orifice which is guarded by the tricuspid valve. Extending between the right sides of the superior and inferior caval orifices there is a prominent muscular ridge, the *crista terminalis* (Figure III-8), which underlies the sulcus terminalis. As the crista terminalis extends caudally it becomes less distinct. Its general course is continued by the valve of the inferior vena cava. Cephalically the crista terminalis passes to the right of the orifice of the superior vena cava, and continues as a muscular ridge which forms the sinistral margin of the opening into the *right auricular appendage* (Figure III-9). This appendage projects cephalically from the right

atrium (Figure III-8) and lies in contact externally with the ascending aorta (Figure III-1). The interior of the right auricular appendage is trabeculated by muscular bands, the *pectinate muscles*. These appear to arise from the most cephalic part of the crista terminalis, and radiate out over the inner surface of the auricular appendage, forming the shell-like pattern which has given them their name.

The portion of the right atrium bounded laterally by the crista terminalis and medially by the interatrial septum is smooth-walled, and is called the *sinus venarum cavarum*. It is derived from the enlarged right horn of the sinus venosus of the embryo (Figure II-30). The lower part of the crista terminalis marks the original line of attachment of the upper part of the right sinus valve; the part of the crista lying cephalic to the superior vena cava, on the cephalic wall of the atrium, is derived from the extension of the venous valves, especially the right one, which was known in the embryo as the septum spurium (Figure II-16B). The caudal portion of the right venous valve persists in reduced form as the (eustachian) valve of the inferior vena

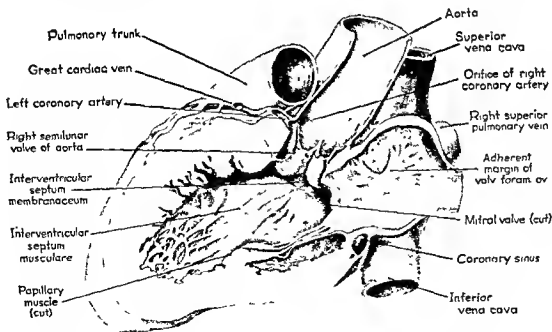


Figure III-10. Left side of the heart opened in a plane approximately parallel to the septa, to show the interior of the left atrium and left ventricle. A segment of the anterior leaflet of the mitral valve has been cut away to expose more fully the region of the membranous portion of the interventricular septum and the aortic orifice.

cava, and the (thebesian) valve of the coronary sinus. These valves vary considerably in size in different individuals and frequently show multiple small perforations. Occasionally lace-like strands from the margins of these valves may project far into the atrial lumen. Usually they are continuous with similar strands inserting into the atrial wall along the line of the crista terminalis. Such a fibrous meshwork represents an incomplete resorption of septum spurium and the right venous valve. When extensive, it presents a highly characteristic appearance and is known as Chiari's net (Figure VI-25, page 288). The left valve of the sinus venosus usually disappears by blending with the interatrial septum. In rare instances remnants of its upper portion may be found closely adherent to septum secundum, or even extending across the limbus fossae ovalis to lie against the valvula foraminis ovalis (Figure VI-26 page 288). In rare instances there may be lace-like remains of the extreme lower portion of the left valve which may show some continuity with remnants of the right valve around the coronary sinus.

The orifice of the superior vena cava is directed caudally and is unguarded by any valve. Across the inner face of the dorsal wall of the sinus venarum there is a transverse muscular ridge of variable prominence—the *tuberculum intervenosum* (of Lower). Opening into the right atrium, particularly upon its septal and lateral walls, are numerous small openings, the *foramina venarum minimarum* (thebesii).

Left Atrium. The left atrium is situated to the left of, and somewhat dorsal to, the right atrium. It lies dorsal to the root of the aorta, and its auricular appendage protrudes to the left of the pulmonary trunk. Opening into the dorsal wall of the left atrium are the right and left superior and inferior pulmonary veins. The orifices of these four veins are not guarded by valves. The left atrioventricular ostium, guarded by the mitral valve, lies on the ventral side of the atrium, facing slightly caudally and to the left. The inner face of the left atrium is relatively smooth, but the inner surface of the left auricular appendage is dis-

tinguished by well-marked pectinate muscles. The peculiar structure of the auricles will be described under Histology of the Heart.

Left Ventricle. In the adult the left ventricle has the form of a narrow cone, tapering to form the apex of the heart. The left ventricle forms the gently curved left cephalic border of the heart (margo obtusus), about half of the diaphragmatic surface, and a small part of the sternocostal surface.

The greater part of the inner surface of its wall is thrown into myocardial ridges of variable size. These ridges (*trabeculae carneae*) may either stand out in relief, or be undercut so that they form muscular bands completely covered by endocardium. In general the myocardium of the left ventricle consists of an outer zone of relatively solid muscle that makes up about two-thirds of its thickness, while its inner third is trabeculated.

In the heart of the fetus and the newborn infant the left ventricular wall is no thicker than the right, and the interventricular septum forms a nearly straight partition between the two ventricular cavities. However, after birth, with the complete separation of the pulmonary and the systemic vascular circuits, the left ventricular myocardium begins to assume its characteristic preponderance. By the fourth year, the adult proportions are attained and the left ventricular wall has approximately twice the thickness and three times the mass of the right (Müller, 1883).

Right Ventricle. In contrast with the wall of the left ventricle, the trabeculated part of the right ventricular wall makes up approximately two-thirds of its thickness and only its outer third is solid. The cephalic part of the right ventricle leading into the pulmonary trunk is called the *pulmonary cone* (Figure III-8), and is delimited from the rest of the right ventricular cavity by a muscular ridge, the *supraventricular crest* (*crista supraventricularis*). The main portion of the right ventricular chamber is crescentic in cross section, since the interventricular septum is concave on its left side and convex on its right (Figure III-12).

Interventricular Septum. The interventricular septum is thick and muscular except for a

small area of connective tissue (*pars membranacea*), near the root of the aorta (Figures III-10, III-20 and III-22). From the left, this membranous portion can be seen to lie in the angle between the attachments of the right and the noncoronary cusps of the aortic semilunar valve. On the right side, the *pars membranacea* is partly concealed by the septal cusp of the tricuspid valve, the attachment of which courses across it near its atrial margin (Figures III-8 and III-26). The part of the septum membranaceum above the attachment of the septal leaflet of the tricuspid valve

is, therefore, atrioventricular, since it lies between the right atrium and the left ventricle (Figure III-11). The membranous portion is the last part of the ventricular septum to be formed embryologically, and is of especial interest clinically since it is the most common site of interventricular defects. It is often referred to by British authors as the "undefended space."

On the left ventricular face of the septum one can occasionally make out the course of the fibers of the left branch of the atrioventricular bundle (of His), as they fan out im-

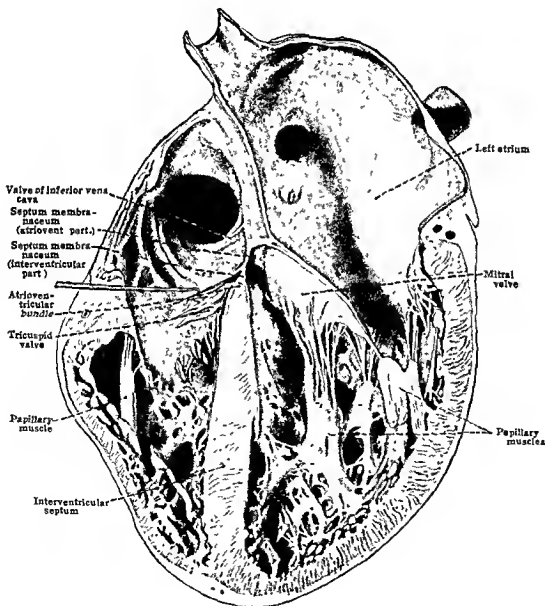


Figure III-11. Frontal section through a heart fixed in diastole, showing a ventral view of the dorsal portion. The plane of section passes through the septum membranaceum and both atrioventricular ostia. (After Tandler. From Morris' *Human Anatomy*, courtesy of Julius Springer and The Blakiston Company.)

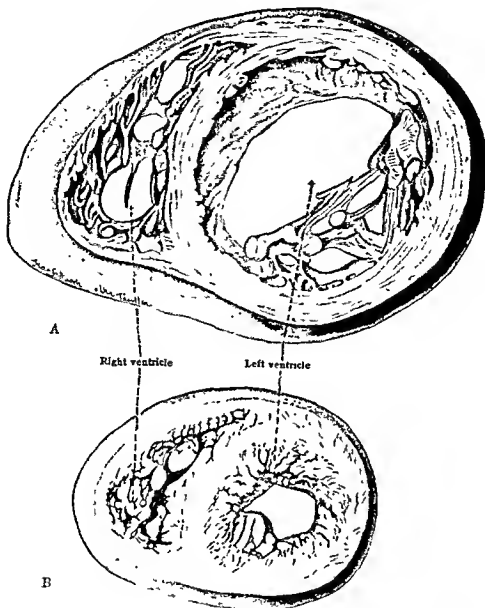


Figure III-12 Sections of the heart cut through the ventricles to show their change in configuration during contraction (After Tandler. From Morris' *Human Anatomy*, courtesy of The Blakiston Company, Philadelphia)

mediately beneath the endocardium. These bundles of fibers can be seen to emerge at the apical margin of the septum membranaceum (Figure III-27). It is known from microscopic study that these fibers of the left branch of the bundle of His spread out in flattened fascicles over the interventricular septum musculare. However, their extent and precise course cannot be determined with certainty by gross inspection, since these specialized fibers are macroscopically indistinguishable from bundles of typical cardiac muscle of the interventricular septum.

A large muscular trabecula is sometimes

found to extend from the septal wall of the right ventricle to the base of the anterior papillary muscle. This is called the *moderator band* (Figure III-9). When this band is present it regularly contains a part of the right branch of the atrioventricular bundle. The moderator band is clearly distinguishable in the hearts of some persons, while in others it appears as a prominent ridge (*crista septo-marginalis*), and in still others is not differentiated at all.

Papillary Muscles. Two papillary muscles of the right ventricle are relatively constant in position, a large anterior papillary muscle,

and a smaller papillary muscle of the conus (of Luscha) (Figure III-8). The *anterior papillary muscle* is situated on the ventral wall of the right ventricle near its junction with the septal wall. The *papillary muscle of the conus* lies just below the septal end of the crista supraventricularis (Figure III-8). A group of *posterior papillary muscles* which are inconstant in number and position arise from the diaphragmatic wall of the ventricle. Some chordae tendineae stretch directly from the septal wall, with or without papillary elevations at their base, to the septal leaflet of the tricuspid valve. The chordae tendineae from the anterior papillary muscle run to the ventral and dorsal leaflets, those from the papillary muscle of the conus run to the septal and ventral, and those from the posterior papillary muscles run to the septal and dorsal leaflets of the tricuspid valve. In the left ventricle there are two large papillary muscles of relatively constant position—the anterior and posterior. Both of these send chordae tendineae to each of the leaflets of the mitral valve.

Atrioventricular Valves. The atrioventricular valves are attached around the orifices leading from the atria into the ventricles and their leaflets extend into the cavities of the ventricles. Each valve has a continuous line of attachment, but its free edge is notched, partially subdividing it into leaflets or cusps (Figure III-19). The right atrioventricular valve is usually divided into three leaflets and is, therefore, called the *tricuspid valve*. The left atrioventricular valve is similarly divided, but into two leaflets and is called the *bicuspid* or, from its fancied resemblance to a bishop's miter, the *mitral valve*. The depth of the notches in both of these valves is extremely variable, and there may be an increase or, more rarely, a decrease in the number of leaflets. Each valve leaflet is attached to the ventricular papillary muscles or directly to the ventricular wall by fibrous cords, the *chordae tendineae*, which are generally branched and of varying thickness. The thinnest cords are attached to the free edge of the leaflet, those of intermediate thickness to its ventricular surface a few millimeters from

its free margin, and the thickest are attached to the ventricular surface near the attached border of the leaflet. The valves are smooth and glistening on their atrial aspect but, because of the attachment of the chordae tendineae, are irregular and fasciculated on their ventricular surface (Figures III-21 and III-22). The leaflets of the mitral valve are called *ventral* (anterior) and *dorsal* (posterior). Those of the tricuspid are called *anterior*, *posterior*, and *medial* (ventral, dorsal, and septal) (Figure III-19). Each leaflet receives chordae tendineae from more than one papillary muscle, and each papillary muscle sends chordae tendineae to more than one valve leaflet. The chordae tendineae of the mitral valve are heavier than those of the tricuspid. The chordae tendineae and papillary muscles combine to prevent the leaflets of the atrioventricular valves from being forced back into the atria by the pressure built up in the ventricles during systole. Contraction of the papillary muscles, along with the rest of the ventricular musculature, prevents a slackening of tension on the chordae tendineae which would otherwise occur when the ventricular cavity becomes smaller during ventricular systole.

Semilunar Valves. The outlet of each ventricle is guarded by three semilunar valve cusps, each of which is a pocket-like flap of connective tissue, covered by endothelium and attached to the annulus fibrosus of the aorta or the pulmonary trunk. The free edges of these cusps are directed away from the ventricle, and in the center of each there is a small fibrocartilaginous *nodule*, the *corpus arantii*. Radiating from this nodule over the fundus of the cusp and extending to its attached margin are *fibrous thickenings*. On either side of the nodule the free edge of each cusp is thin, forming a pair of crescentic areas called the *lunulae* (Figures III-10 and III-22).

There are two widely employed systems of naming the cusps of the semilunar valves. If they are named according to their relative positions when the heart is *in situ* in the thorax, as is done in one system, the aortic valves are named *right posterior*, *left posterior*, and *anterior*; while those of the pulmo-

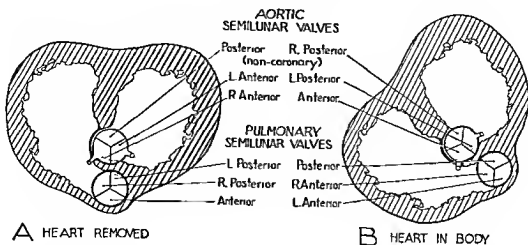


Figure III-13. Diagrams showing the bases for the two common systems of naming the semilunar valves. A, based on a removed heart oriented with its ventricles to the right and left of the septum. This is the B.N.A. system. B shows the names of the cusps, based on their relative positions with the heart *in situ* in the adult thorax. This is the L.N.A. system.

nary trunk are named *right anterior*, *left anterior*, and *posterior* (Figure III-13B). However, if the heart is removed from the body and held so that the ventricular septum forms its median plane, the pulmonary trunk lies almost directly ventral to the aorta, and the valves of the pulmonary trunk are named *right posterior*, *left posterior*, and *anterior*; while those of the aorta are named *right anterior*, *left anterior*, and *posterior* or *noncoronary* (Figure III-13A). This latter terminology, although not consistent with the axes used in naming some other regions of the heart, is convenient in that it corresponds to

the naming of the right and left ventricles, and the right and left coronary arteries. It is also the more logical from a developmental point of view.

The aortic semilunar valves are stronger than those of the pulmonary trunk, as might be expected from the higher pressure in the aorta. Opposite these aortic semilunar valves, the aortic wall bulges out into three corresponding dilations, called the *aortic sinuses* (sinuses of Valsalva) (Figure III-22). The right and left coronary arteries arise from the upper part of the right and left aortic sinuses, respectively (Figure III-19).

THE BLOOD VESSELS OF THE HEART

Coronary Arteries. The *left coronary artery* arises in the wall of the left sinus of Valsalva and runs laterally and ventrally between the root of the pulmonary trunk and the left atrium. After a short distance it branches into two vessels, the *anterior descending branch*, which courses caudally in the anterior longitudinal sulcus to reach the apex of the heart, and the *circumflex branch*, which swings around the base of the left atrium, in the coronary sulcus, to reach the diaphragmatic surface of the heart (Figure III-14). In its course the anterior descending branch sends perforating rami into the substance of the interventricular septum and into the adjacent ven-

tricular myocardium. The circumflex branch gives off a ramus which runs down over the *margo obtusus* toward the apex of the heart, and also sends off many other smaller arteries to supply the root of the aorta, left atrium, and left ventricular wall. To the left of the posterior longitudinal sulcus, adjacent to the coronary sinus, the circumflex branch anastomoses with small arteries from the right coronary artery (Figure III-16).

The *right coronary artery* arises from the right aortic sinus and passes laterally in the groove between the pulmonary cone and the right atrium (Figure III-15). It then sweeps, in the coronary sulcus, around the

of the right atrium to reach the posterior longitudinal sulcus. At this point it divides, giving a large branch along the length of the posterior longitudinal sulcus which is known as the *posterior descending branch*, and a smaller branch to anastomose, adjacent to the coronary sinus, with the circumflex branch of the left coronary artery (Figure 16). The first ventricular branch of the left coronary artery passes to the musculature of the pulmonary cone. This has been reported to arise independently from the right sinus of Valsalva in one-half of a series of adult hearts (Schlesinger, Zoll and Wessler, 19). In its course the right coronary artery gives off two sizable branches, one to run along the *margo acutus*, the *right marginal*, and another to pass over the ventral wall of the right ventricle, the *preventricular* (Figure 14). It also gives off smaller branches to supply the roots of the aorta, the pulmonary trunk, and the right atrium. A small but con-

stant branch passes between the right auricular appendage and the superior vena cava to course along the *sulcus terminalis*. This branch is of importance since it lies along the axis of the sinoatrial node. The posterior descending branch gives off perforating rami to supply the muscle of the interventricular septum and the adjacent ventricular walls.

The study of the terminal branches of the coronary arteries of the human heart by means of gross dissection, even of well-injected specimens is laborious and necessarily incomplete. In recent years a method has been devised in which the coronary arteries are injected with a radiopaque medium. Following this injection the heart is cut and "unrolled" or flattened out, so that a roentgenogram may be made of the entire arterial pattern of the walls of both ventricles and part of the atria. The interventricular septum may be cut free at its attached borders and photographed on the same x-ray film to give a com-

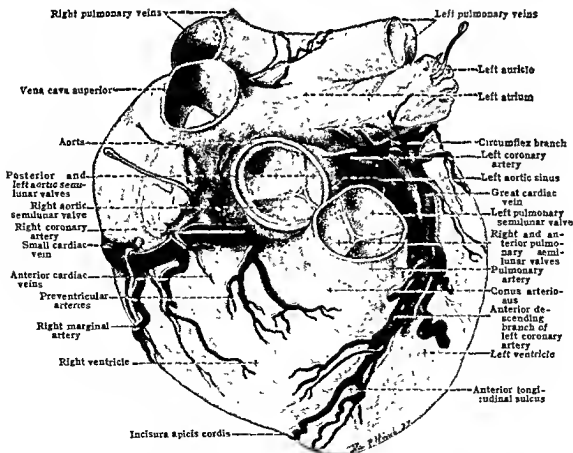


Figure 14. Cephalic view of the heart with the epicardium removed to expose the injected coronary vessels. (After a dissection by R. F. Blount. The original drawing by Jean Hirsch has been slightly modified. From Morris' *Human Anatomy*, courtesy of The Blakiston Company.)

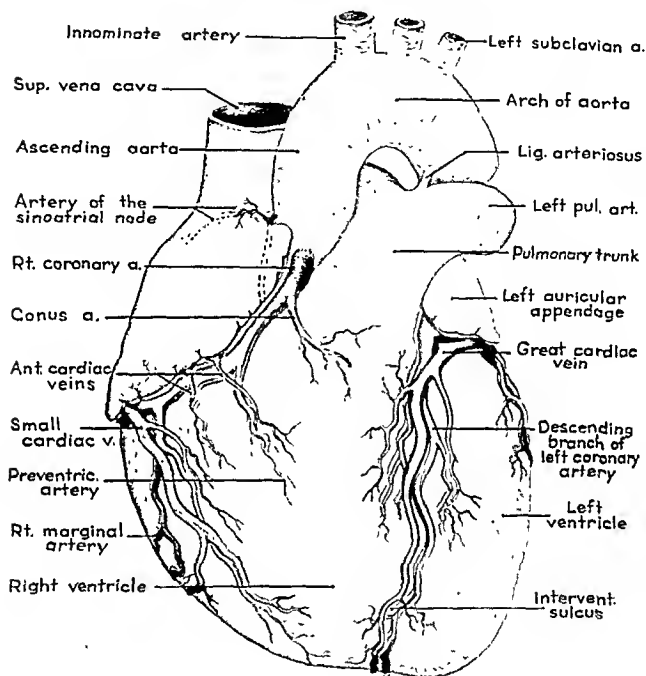


Figure III-15. Ventral view of heart, with epicardium removed to expose the injected coronary vessels.

plete picture of the arterial supply of the entire ventricular myocardium (Schlesinger, 1938; Salans and Tweed, 1947). Such studies show that adult human hearts vary considerably with respect to the relative distribution of the branches of the right and left coronary arteries. Hearts may be classified into one of three groups, according to whether the right or left coronary arteries predominate. Group I consists of hearts in which the right coronary predominates; in Group II

the right and left coronaries are balanced in distribution, and in Group III, the left coronary is dominant. In a study by Schlesinger (1940), Group I made up 48 per cent of a series of 225 adult hearts; Group II, with a balanced circulation, made up 34 per cent; and the remaining 18 per cent fell in Group III, with a predominant left coronary artery. It is of interest that the dominant artery supplied nearly all of the musculature of the interventricular septum.

Coronary Veins. The coronary veins lie parallel to the branches of the coronary arteries and return the blood to the right atrium by way of the coronary sinus. In general they lie in the fat-laden connective tissue of the epicardium, somewhat superficial to the arteries.

The *great cardiac vein* originates in the epicardium of the anterior longitudinal sulcus (Figure III-14). When it reaches the coronary sulcus it swings dorsally and, within it, courses around the base of the left atrium in company with the circumflex branch of the left coronary artery. It empties into the distal end of the coronary sinus beneath the left inferior pulmonary vein (Figure III-16). At this point there is usually a pair of valves. In its course it receives from the walls of the left atrium and ventricle tributaries, most of

which are guarded by valves at their points of confluence with it.

The *middle cardiac vein* runs in the posterior longitudinal sulcus in company with the posterior descending branch of the right coronary artery. It receives blood from the septum and the ventricular walls and empties into the coronary sinus near the opening of the coronary sinus into the right atrium. Its orifice is usually guarded by a single valve.

The *small cardiac vein* lies in the coronary sulcus at the base of the right atrium. Through much of its course it parallels the right coronary artery. It receives tributaries from the walls of the right atrium and ventricle and empties into the coronary sinus near its entrance into the right atrium (Figure III-16).

The *posterior vein of the left ventricle* runs over the dorsal aspect of the ventricle to

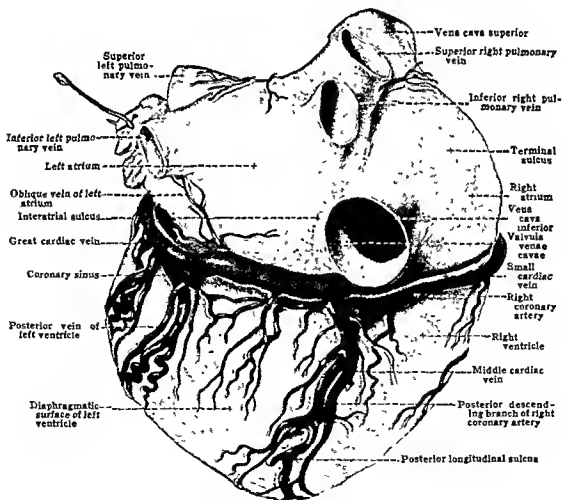


Figure III-16. Dorsocaudal view of the heart with the epicardium removed to expose the injected coronary vessels. (After a dissection by R. F. Blount. The original drawing by Jean Hirsch has been slightly modified. From *Morris' Human Anatomy*, courtesy of The Blakiston Company, Philadelphia.)

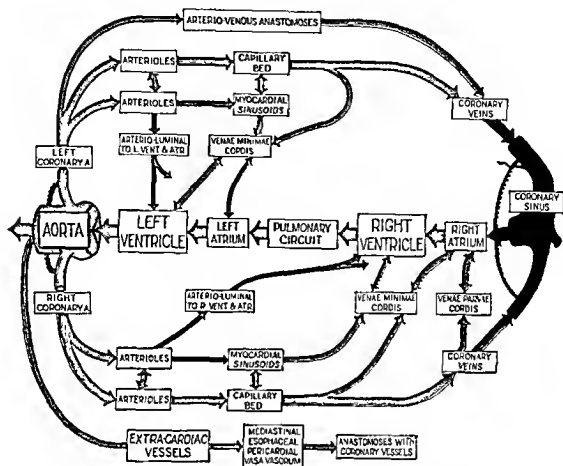


Figure III-17. Schematic plan indicating the interrelations of the various vascular channels supplying the walls of the heart. (Developed in collaboration with Dr. Richard Lieata.)

empty into the coronary sinus near its distal end. There are similar small unnamed veins draining the diaphragmatic surface of the left ventricle and discharging into the coronary sinus.

The anterior cardiac veins lie on the ventral aspect of the right ventricle, and empty either into the small cardiac vein or directly into the right atrium (Figure III-14). These veins are often called the *venae parvae* of the heart.

There is a small vein that passes down over the dorsal wall of the left atrium, lateral to the left pulmonary veins, and empties into the distal end of the coronary sinus. This is the *oblique vein of the left atrium* or vein of Marshall (Marshall, 1850). It is highly variable in size, and represents the left common cardinal vein of the embryo (Figure II-30). It is this vessel which is the terminal portion of a left superior vena cava, when such a vessel persists (see Figure VI-153, page 482).

The *coronary sinus* lies in the coronary sulcus along the diaphragmatic surface of the heart (Figure III-16). It empties into the right atrium through an opening that is partially guarded by an incompetent valve flap, the *thebesian valve* (Figure III-8). The coronary sinus, accompanied by the circumflex branch of the left coronary artery, is embedded in the fatty connective tissue of the coronary sulcus. Its adventitia usually contains small spiralling fascicles of cardiac muscle that blend with those of the left atrium (Figure III-21).

The Intramural Circulation. The myocardium is richly supplied with small vascular channels. There is an extensive web of capillaries which course among the cardiac muscle fibers and lie in intimate contact with them. These capillaries are fed by branches of the various coronary arteries, and are drained in part by the coronary veins whose epicardial pattern has been described above. However,

there is a peculiarity of the intramyocardial circulation which deserves particular attention. Careful injection studies show that there are anastomosing vessels which run between adjacent branches of the same coronary artery, between branches of the right and left coronary arteries, between the coronary arteries and the coronary veins, and between branches of the coronary veins (Figure III-17) (Schlesinger, 1938, Gross, 1921, Prinzmetal *et al.*, 1947, 1948). It seems probable that in the normal heart of a young person these anastomoses are small, since it is well known that in case of sudden occlusion, branches of the coronary arteries behave as end arteries and their occlusion leads to infarction of the myocardium. Nevertheless,

these anastomoses are capable of gradual enlargement, and in many hearts may be found to be functionally of significant caliber. In addition, the intramyocardial vascular pattern exhibits another peculiarity: there are channels which pass from the arterioles, from the capillary bed, and from the coronary veins directly into the lumen of the heart (Figure III-18). These venous connections with the cardiac lumen have been described for many years as the *thebesian veins* (Thebesius, 1716). The connections between the coronary arteries and the cardiac chambers, called *arterio-luminal vessels*, have been found more recently (Wearn, 1928a; Wearn *et al.*, 1933). Since the walls of the ventricles are thrown into trabeculae, these arterio-luminal vessels

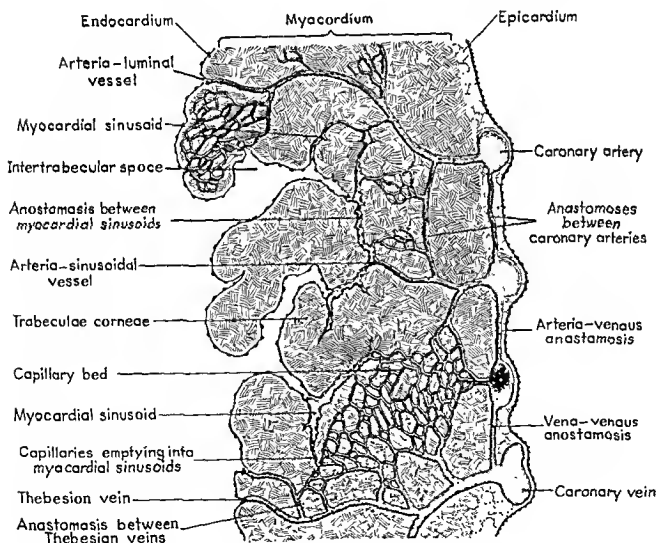


Figure III-18. Diagram of the ventricular wall, showing the relationship between the various intramural vascular channels.

may empty either at the surface of the trabeculae or, as is more usual, into the intertrabecular spaces.

The arterio-luminal vessels have the histologic characteristics of venous channels when they pass through the endocardium. At a variable depth within the myocardium they acquire the muscular coat typical of an artery. Accordingly, these arterio-luminal vessels may reasonably be regarded as *venae minimae cordis* (thebesian veins) which are connected directly to the coronary arteries by means of arterio-venous anastomoses of arteriolar caliber.

Deep within the myocardial musculature there is, in addition to the capillary bed (Wearn, 1928b), a richly anastomosing network of thin-walled irregular channels which have been called *myocardial sinusoids*. These sinusoids receive vessels from the coronary arteries and the capillaries, and communicate with the coronary veins. From their developmental history, these myocardial sinusoids may be regarded as intertrabecular spaces of much reduced caliber. If they are so re-

garded, their interconnections with the coronary vessels and their continuity at the same time with the intertrabecular spaces of the lumen of the heart are reasonable and consistent. Figure III-18 shows these interrelationships in schematic form.

The Lymphatics. There are two networks of lymphatics in the heart, one in the endocardium and the other in the epicardium. The endocardial network drains through channels in the myocardium into the lymphatics of the epicardium. The epicardial meshwork of channels, containing many valves, drains toward the atrioventricular sulcus by means of several longitudinal channels which run for the most part parallel to the coronary veins in the anterior and posterior longitudinal sulci of the ventricles. These trunks unite and course in the coronary sulcus to the region of the root of the pulmonary trunk. Thence they pass along the dorsal aspect of this trunk and leave the pericardial cavity to empty into one of the bronchial lymph nodes and join the lymphatic drainage system of the mediastinum.

THE FIBROUS FRAMEWORK OF THE HEART

The *Annuli Fibrosi*. In the adult heart, the atrial myocardium is completely separated from that of the ventricles, except for their connection by way of the main atrioventricular conduction bundle (bundle of His). The material which effects this separation consists of a fibrous framework which at the same time gives attachment to the atrial and ventricular musculature. This fibrous framework (cardiac "skeleton," or fibrous base) of the heart is formed essentially by four rings of densely woven, collagenous fibers and the connective tissue which holds them in their characteristic relationship to each other. These rings, called the *annuli fibrosi*, surround the two atrioventricular ostia, the aortic outlet from the left ventricle, and the outlet of the pulmonary trunk from the right ventricle. These annuli not only serve as bases for the insertion of the atrial and ventricular musculature, but also constitute the lines of attach-

ment of the mitral, tricuspid, and semilunar valves (Figures III-21, III-22, and III-24). Throughout most of their circumference, the *annuli fibrosi* encircling the atrioventricular ostia are in the form of compact rings of fibrous tissue of relatively small cross-sectional area. The aortic and pulmonary annuli, however, are essentially short, robust tubes rather than rings (Figure III-19). The semilunar valves are attached to the distal margins of these tubular annuli. Thus each annulus is scalloped, matching the contours of the bases of the semilunar valves. The aortic and pulmonary annuli can be visualized as resembling three-pointed royal crowns. The pulmonary annulus is attached to the aortic by a moderately distinct band of heavy fibers, called the *conus ligament*.

The *Fibrous Triangles*. The fibrous framework of the heart is most massive in the space which is bounded by the right and left atrio-

ventricular annuli and the aortic annulus. This area is called the *right fibrous triangle* or *trigone* (Figure III-19). The *left fibrous triangle*, smaller than the right, lies in the angle between the aortic and the left atrioventricular annuli. It is the dense fibrous tissue of the right fibrous triangle that with increasing age may acquire an almost cartilaginous character reminiscent of the cartilage and bone that develop in this region of the hearts of some ungulates. Through the right fibrous triangle passes the only normal connection between the atrial and ventricular musculature, the atrioventricular conduction bundle.

The Septum Membranaceum. That part of the wall of the aortic outlet from the left ventricle which extends from the muscular interventricular septum below, to the bases of the noncoronary and right anterior cusps of the aortic semilunar valves is distinguishable by its thin, nonmuscular character, and is called the *septum membranaceum* (Figure III-10). This septum is formed of densely-woven, collagenous fibers and has essentially

the same histologic character as the annuli fibrosi. The line of attachment of the septal leaflet of the tricuspid valve courses obliquely across the right face of the septum membranaceum, dividing it into two parts (Figures III-11 and III-25). The part which lies below the attachment of the valve separates the right from the left ventricular cavities. For this reason it is called the *interventricular part* of the septum membranaceum. The portion of the septum membranaceum that lies above the valve attachment separates the right atrium from the left ventricle and is called its *atrioventricular part* (Figure III-22).

Thus the septum membranaceum lies in a plane that is essentially at right angles to the plane of the right and left atrioventricular annuli fibrosi (Figure III-20). When viewed from above, as in Figure III-19, the septum membranaceum is seen on edge, and forms the right anterior corner of the right fibrous triangle. The term "right fibrous triangle" is misleading since the area thus designated

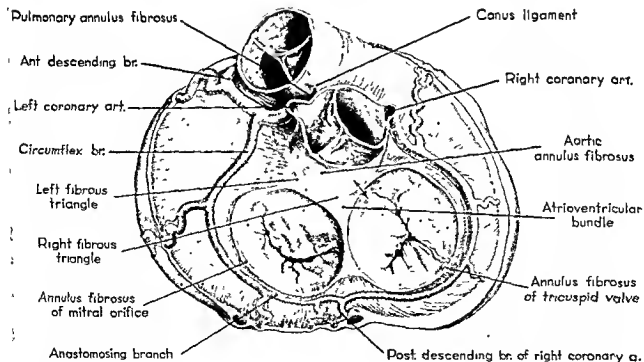


Figure III-19. Ventricular portion of the heart viewed from above with the atria removed, to show the fibrous triangles, the annuli fibrosi and the attachment of the ventricular musculature to them. The fatty epicardium has been removed from the atrioventricular sulcus in order to show the coronary arteries.

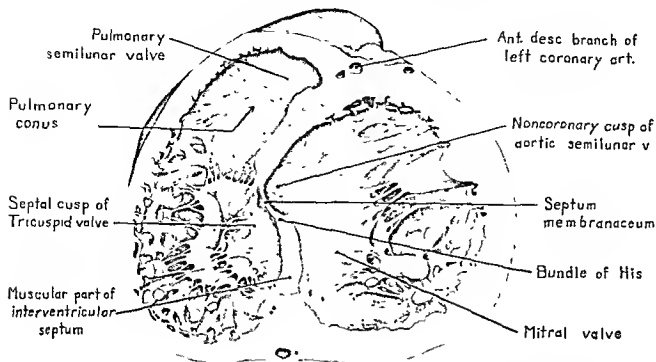


Figure III-20. Interior of the ventricular base of the heart, exposed by removal of the apical half of the ventricles. The interventricular septum has been partially cut away to show the relations of the interventricular septum membranaceum, and the mitral, the tricuspid, and the aortic valves.

appears triangular only when seen directly from above. It actually represents a fusion between the right and left atrioventricular

annuli fibrosi, the aortic annulus fibrosus, and the septum membranaceum.

THE HISTOLOGY OF THE HEART

The Endocardium. All the cavities of the heart are lined with a simple squamous epithelium called endothelium. This delicate lining is supported by a layer of fibroelastic connective tissue. The endothelium and its subjacent connective tissue make up the endocardium. The connective tissue of the endocardium tends to be differentiated into a subendothelial layer of delicate collagenous fibers and a deeper layer with abundant elastic fibers. In it are found a few blood and lymph capillaries and the vessels connecting the intra-myocardial channels with the lumen of the heart, such as arterio-luminal vessels and the *venae minimae cordis*. A rudimentary layer of smooth muscle can often be found in the endocardium of both atria and ventricles. The endocardium of the atria is markedly thicker than that of the ventricles (Figures III-21 and III-22). It usually contains some-

what more smooth muscle although, even in the atria, the amount of smooth muscle is so small as to be of questionable functional significance. In the region of the base of the heart the endocardial connective tissue is continuous with the fibrous framework (Figure III-21).

The Myocardium. The myocardium of the heart wall consists of cardiac muscle and its supporting connective tissue. The fibers of the atrial myocardium are attached to the annuli surrounding the two atrioventricular ostia (Figures III-21 and III-22). The more superficial of these fibers either encircle both atria or enter the interatrial septum to form a figure-eight pattern about both atrial cavities. The deeper fibers are attached to only one annulus and encircle one atrium only.

The ventricular myocardium is complex in arrangement. It consists of interwoven

bundles and bands of muscle fibers which are partially separated from each other by fibro-elastic connective tissue, and are distinguishable by their orientation (Robb and Robb, 1942). In general, the fiber-bands of the layer nearest the endocardium have a course almost at right angles to that of the most superficial

fiber-bundles of the same area (Figure III-24). The intervening fiber-bundles exhibit all degrees of intermediate obliquity. All of these bands of cardiac muscle arise from, and insert into, the fibrous framework of the heart. Their attachment for the most part is directly into the fibrous base of the heart. Certain

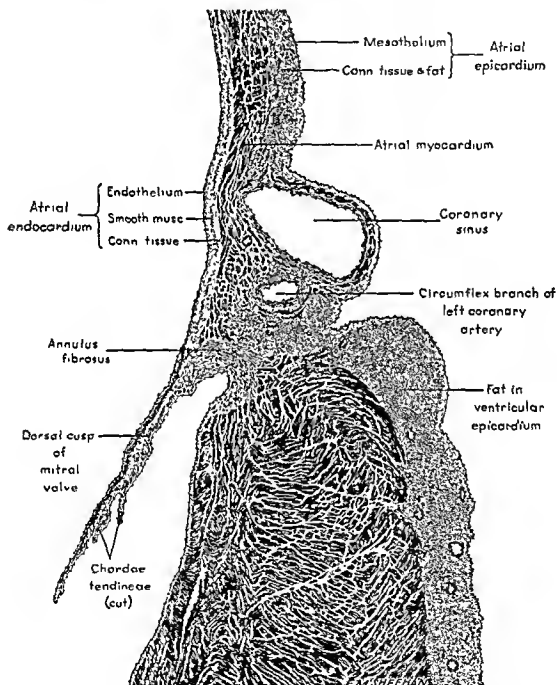


Figure III-21. Projection drawing (X8) of a section through the dorsolateral wall of an adult human heart. The section passes through the coronary sulcus and shows the left atrial wall above and the left ventricular wall below the dorsal (posterior) leaflet of the mitral valve (cf. Figures III-10 and III-10). The section was taken far enough dorsally to pass through the coronary sinus rather than the great cardiac vein (cf. Figure III-16).

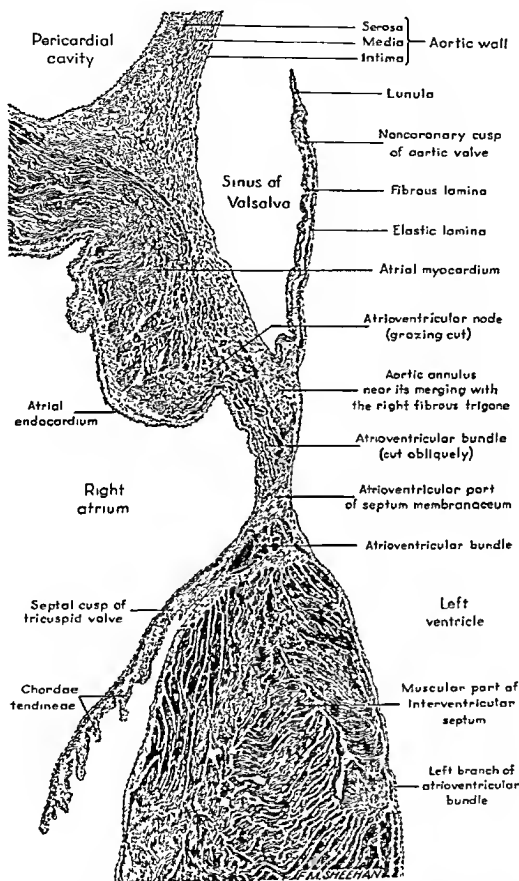


Figure III-22. Projection drawing (X8) of a section through the septum membranaceum of an adult human heart. The section was taken at such an angle that it passes through the aortic outlet, cutting the noncoronary cusp of the aortic valve (cf. Figure III-19). Note the location of the atrioventricular bundle lying at the transition from the membranous to the muscular part of the interventricular septum.

fiber-bundles, however, may attach to the fibrous skeleton of the heart indirectly by means of the chordae tendineae and atrioventricular valves. The cardiac muscle fibers are invested by a layer of delicate reticular and collagenous fibers which make up the *endomysium*. The groups of muscle fibers are partially set apart from adjacent bundles by more dense layers of fibroelastic connective tissue called the *perimysium*. This perimysial connective tissue is continuous with the endomysium, and its fibers blend with those of the endocardium and the epicardium to weld the heart wall into a coherent unit. It is in the perimysium and the endomysium that one finds the network of blood and lymph capillaries and the myocardial sinusoids which have been described (Figure III-18). In routine preparations, most of the smaller blood channels of the myocardium are not filled with blood. It is, therefore, difficult to appreciate the extraordinary richness of the finer vessels unless special efforts have been made to inject them before fixation.

The individual muscle fibers are branched and anastomose to such a degree (Figure III-28) that it is meaningless, either morphologically or physiologically, to attempt to state their length. Their diameter varies, that of fibers of the typical ventricular myocardium averaging about 12 micra in fixed material. The surface layer of the fiber is a delicate membrane called the *sarcolemma* which is in immediate contact with the endomysium. Within the sarcolemma is the *sarcoplasm* serving as a matrix for *myofibrils*. These myofibrils are coarse and give the cardiac muscle fibers a longitudinally fibrillated appearance. The myofibrils tend to clump together in fixed material so that in cross-section the muscle fibers tend to show a cart-wheel pattern. The myofibrils are not optically homogeneous, but exhibit dark (anisotropic) and light (isotropic) areas along their length. These areas tend to line up across the diameter of the fiber, giving it a cross-striated appearance. There are also thin bands, particularly well-stained with iron hematoxylin, which run across the muscle fibers either straight or in a step-wise manner. These are the *intercalated disks*. It was

formerly the consensus that these structures did not represent the boundaries between separate cells and that cardiac muscle, therefore, was to be regarded as a true syncytium. Recent studies with the electron microscope, however, seem to indicate that the intercalated disks may well represent modified cell boundaries. These same studies show an anchorage of the individual myofibrilli to either side of the intercalated disks.

The conduction system of the heart is formed from cardiac muscle fibers which differ somewhat in their detailed structure from the "typical" muscle described above. The histology of these fibers will be considered later, after the course of the conduction system has been discussed.

Auricles. The structure of the thin-walled auricles (auricular appendages) of the two atria show striking differences from that of the typical atrial wall. The bulk of the auricular myocardium is arranged in relatively large trabeculae, called *pectinate muscles*, because of their vague resemblance to the ridged pattern of a scallop shell. The myocardium between these trabeculae is extremely thin. In some areas it is in the form of a loose network of anastomosing bundles of cardiac muscle. Through the interstices of this network there is continuity between the connective tissue of the endocardium and the epicardium. The lumen of the auricles is lined with endocardium which usually has the thickness typical of that of the atrium, in distinction from that of the ventricles. The epicardium is composed of relatively fine fibroelastic connective tissue, containing variable amounts of fat. In this epicardial tissue course the small coronary arteries and veins supplying the auricular wall. One striking characteristic of the auricles is that these epicardial vessels can be seen to communicate directly with the intertrabecular spaces between the pectinate muscles. This communication is by means of endothelially lined channels that pass through the spaces in the network of myocardial bundles of the wall (Figure III-23). Thus there are relatively large arterio-luminal and veno-luminal channels in the auricles. This configuration is strongly remi-

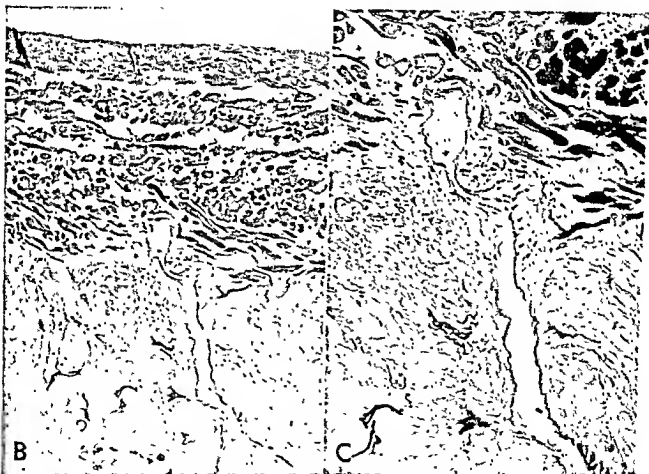
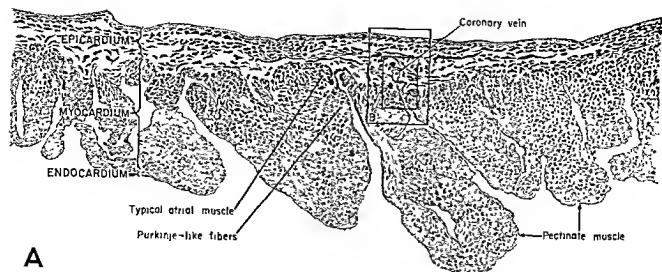


Figure III-23. A. Topographic diagram of auricular wall showing the locations of photomicrographs B and C. Anastomoses between coronary vessels and intertrabecular spaces are indicated by an asterisk (*). B and C. Photomicrographs showing in more detail an anastomosis between a coronary vein and an intertrabecular space. Note also the subepicardially located "typical" atrial muscle as contrasted with the paler and larger Purkinje-like fibers in their characteristic position nearer the lumen. B, X 115, C, X 220.

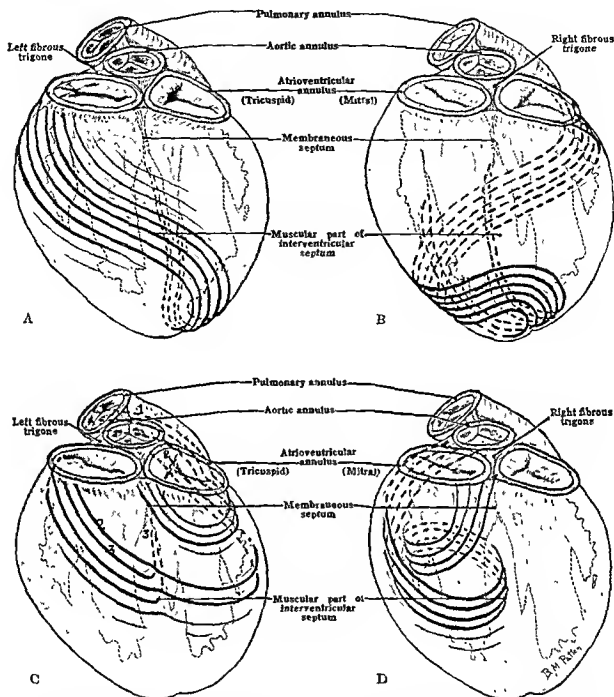


Figure III-24. Diagrams illustrating schematically the courses followed by some of the major groups of ventricular muscle-fibers. (Based on the work of MacCallum, and Tandler, and on original dissections. From Morris' *Human Anatomy*, courtesy of The Blakiston Company, Philadelphia.)

The background of each diagram is a posterior view of the heart drawn as a semitransparent object. The directions followed by the muscle fibers are indicated by red lines which are solid on the side toward the observer and broken on the side away from the observer or where they lie deep in the interventricular septum. A. Fibers starting superficially from the left atrioventricular annulus and ending in the left ventricle. B. Fibers starting superficially from the right atrioventricular annulus and ending in the right ventricle. C. Three groups of deep fibers: 1-1, fibers with a course primarily within the right ventricle; 2-2, fibers common to the deeper layers of both ventricles; 3-3, fibers partly within the deeper layers of the ventricular walls but terminating in the septum. D. Fibers passing through the septum and making a double spiral in the walls of the left ventricle.

niscient of the embryonic condition described in Chapter II for the developing ventricular wall.

Another peculiarity found in the auricular wall is that a large amount of the myocardium is made up of atypical cardiac muscle fibers that have the characteristics of Purkinje fibers (Figure III-23). It should be emphasized that these fibers have no known functional relationship to the sinoventricular conduction system as it is understood at the present time.

The Epicardium. The face of the heart wall which abuts on the pericardial cavity is covered by mesothelium, a simple squamous or cuboidal epithelium. This, with a subjacent layer of fibroelastic connective tissue, constitutes the epicardium (visceral pericardium). The connective tissue of the ventricular epicardium contains a considerable amount of fat, particularly in the region of the sulci and around the larger vascular channels which lie over the surface of the ventricles. It is continuous with the connective tissue forming the serosa of the great vessels entering and leaving the heart. The deeper layer of the epicardial connective tissue is continuous with the perimysium of the myocardium, except where it blends with the dense fibrous tissue of the annuli fibrosi (Figure III-21). In regions where there is no mesothelial layer, such as between the reflections of the pericardium (Figure III-6), the epicardial connective tissue is continuous with that of the mediastinum. The epicardium of the atria is, in general, thinner than that of the ventricles, and contains relatively few, small, coronary vessels. In such thin-walled areas as the aorticles, the epicardium consists of a strikingly compact thin layer of coarse collagenous fibers with but few elastic fibers and sparsely scattered areas of fat (Figure III-23).

The Valves of the Heart. All the valves of the heart have essentially the same basic structure. They consist of a fold of endocardial connective tissue covered by endothelium. The connective tissue is differentiated into two main layers, one associated with each face of the valve. As a convenience in describing valves of the type encountered in the cardiovascular system, they may be said to

have a "holding face" and a "deformed face." The term "holding face" is used to designate the face of a valve against which pressure builds up when the valve is closed. The fibers which predominate in the connective tissue layer of the holding face are coarse collagenous bundles which afford the maximum strength. Since the denseness of the collagenous lamina makes the holding face relatively incompressible, the opposite face of the valve must be stretched as the valve opens and closes. It is, for this reason, called the deformed face. The connective tissue of the deformed face of a valve has fewer and smaller collagenous fiber-bundles and a conspicuous proportion of interwoven elastic fibers. In the case of the atrioventricular valves the holding face is toward the ventricular cavity, and into the dense white fibrous layer constituting it are inserted the collagenous fibers of the chordae tendinae. The endothelial covering of these chordae is continuous with that covering the ventricular surface of the valve (Figures III-21 and III-22). The fibrous layers of the valve are continuous with the fibrous framework of the heart. The continuity of the fibers of the holding face is particularly intimate, giving the valve a strong attachment. There may be small amounts of atrial muscle projecting for a short distance into the base of the atrioventricular valves.

The holding face of the semilunar valves is toward the lumen of the aorta or the pulmonary trunk. These valves have no chordae tendinae, and depend for their strength on the intimate fusion of their densely-woven laminae with the annuli fibrosi (Figure III-22).

The atrioventricular valves from hearts of older persons often are quite richly vascularized (Bayne-Jones, 1917). However, since this vascularization is found most often in hearts of persons with a history of previous endocarditis, and since the valves from hearts of young healthy persons show but a few very small vessels, it seems probable that markedly vascularized atrioventricular valves are not to be regarded as normal, but as the result of previous pathologic change (Kugel and Gross, 1926; Wearn *et al.*, 1936; Koletsky, 1946).

THE SINOVENTRICULAR CONDUCTION SYSTEM

The embryonic myocardium possesses three fundamental properties: inherent rhythmicity, conductivity, and contractility. The myocardium of the adult heart has differentiated functionally along these three lines. There is the tissue making up the nodes of the conduction system which is specialized along the lines of inherent rhythmicity. The muscle making up the bundle of His, its branches, and the so-called Purkinje fibers, is specialized for rapid conductivity. The "typical" muscle forming the greater part of the myocardium of the atria and the ventricles seems to have been specialized in contractility. In spite of

their characteristic specialization in one property, all of these types of heart muscle possess all three of the above basic properties in some degree.

The histology of "typical" cardiac muscle has already been described. In contrast with it, we may characterize the other types of myocardium as "atypical" since, although they possess the basic characteristics of cardiac muscle, these characteristics differ quantitatively and qualitatively from their counterparts in typical cardiac muscle. As will be shown later, the tissues regarded as atypical cardiac muscle differ among themselves as

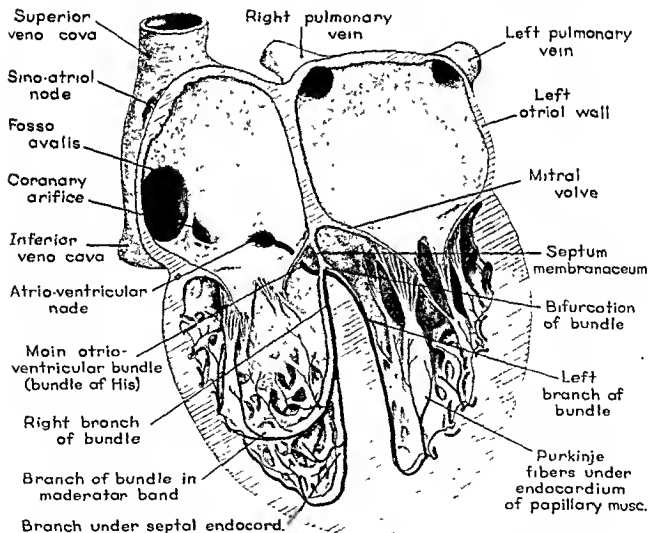


Figure III-25. Schematic diagram of heart opened frontally, with the location and relations of the several parts of the sinoventricular conduction system indicated in red. This figure should be compared with the less schematic views from the right (Figure III-26) and from the left (Figure III-27).

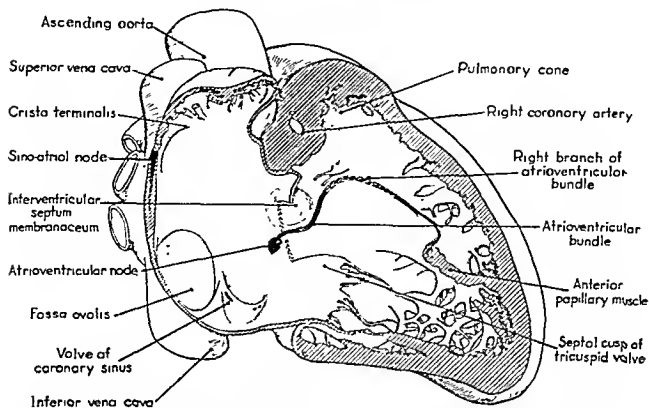


Figure III-26. Simplified diagram of the heart opened from the right as in Figure III-8, to show the location of the sinoatrial conduction system. Where this tissue lies subendocardially, it is shown in solid black, where it lies deep within the myocardium, it is indicated by broken lines.

to their microscopic structure. To a certain extent the atypical cardiac muscle of the conduction system shows some of the morphologic characteristics of embryonic myocardium. It must be emphasized, however, that with this apparent structural simplicity is associated a high degree of physiologic specialization, as indicated, for example, by its high rate of propagation of impulses.

The contraction of the heart is initiated in a mass of nodal tissue lying near the inlet of the superior vena cava. This is the *sinoatrial node* (Figures III-25, and III-26), derived from a portion of the myocardium of the right horn of the sinus venosus of the embryonic heart (Figure II-38). On the basis of present evidence, the excitatory impulse is believed to spread thence over the typical cardiac muscle of the atrium to a second mass of nodal tissue. This is the *atrioventricular node*, lying in the floor of the right atrium. When isolated experimentally, it has a rate of inherent rhythmicity that is slower than that of the sinoatrial node but higher than that of the

myocardium in general. In the intact heart it follows the pace of the faster pulsating sinoatrial node. From the atrioventricular node the impulse passes along the fibers of the *atrioventricular bundle* or *bundle of His*, which conducts ten times as rapidly as does the typical cardiac muscle of the ventricle (Wiggers, 1923). The bundle of His pierces the fibrous base of the heart and normally forms the only myocardial connection between the atrium and the ventricle. At the crest of the muscular portion of the interventricular septum the bundle of His sends branches to the right and left ventricles (Figure III-25). At the end of the ramifications of these branches the fibers attain a different histologic character and are known as *Purkinje fibers*. These fibers are continuous with the typical cardiac muscle fibers, and pass the excitation wave on to them. The entire complex of atypical cardiac muscle which is concerned with the propagation of cardiac contraction is known as the *sinoventricular conduction system*.

The Sinoatrial Node. As indicated in the preceding section, the sinoatrial node lies in the wall of the right atrium in the region of the sulcus terminalis between the right atrium proper and the sinus venarum (Figures III-25 and III-26). It is roughly carrot-shaped and consists of a main mass in the deep part of the crista terminalis near the entrance of the superior vena cava, with a prolongation coursing at least 2 cm. caudally along the sulcus terminalis. It is supplied by a constant small branch, usually of the right coronary artery, which reaches the sulcus terminalis by passing through the notch between the superior vena cava and the right auricular appendage (Figure III-14). This artery is a useful landmark in locating the sinoatrial node since it lies embedded along the axis of the nodal tissue. Some workers have reported cephalic extensions of nodal tissue that partially surround the dorsal and lateral aspects of the orifice of the superior vena cava.

Histologically the atypical cardiac muscle which makes up the sinoatrial node consists of delicate fibers varying between 2 and 7 micra in diameter, loosely interwoven into a snarl of anastomosing strands (Figure III-

28). These fibers are less strongly cross-striated than are those of the typical myocardium, and they possess fewer myofibrils. They can be seen to be continuous with the typical myocardial fibers of the adjacent atrial wall, and the transition between the two is so gradual that no sharp line of demarcation can be established.

Atrioventricular Node. A second mass of similar nodal tissue is found in the floor of the right atrium, to the left of the coronary sinus and adjacent to the base of the interatrial septum immediately above the right fibrous triangle. This is called the atrioventricular node (Figures III-22 and III-26). Except where they extend into the atrioventricular bundle, its fibers are continuous with those of the atrial myocardium without definite line of demarcation. The histologic structure of the atrioventricular node is essentially that of the sinoatrial node, except that the former is more compactly arranged and the fibers are slightly thicker, ranging from 3 to 11 micra in diameter.

The Atrioventricular Bundle. At one point on its inferior margin the fibers of the atrioventricular node gradually become aligned

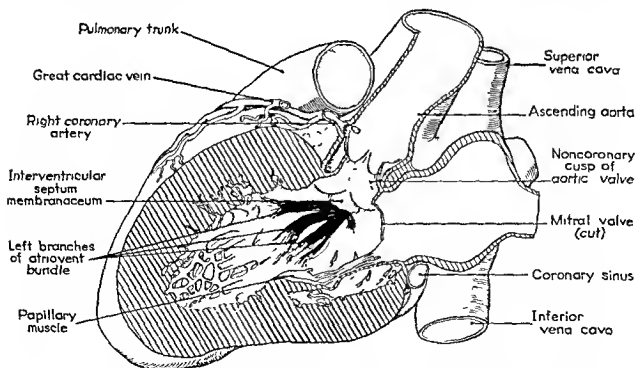
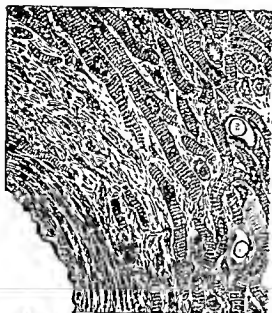


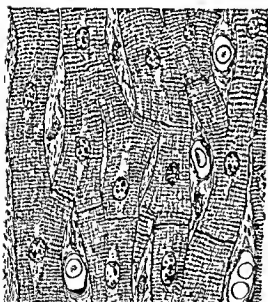
Figure III-27. Simplified diagram of the heart opened from the left, as in Figure III-10. The solid black indicates the position of the left branches of the atrioventricular bundle (of III).



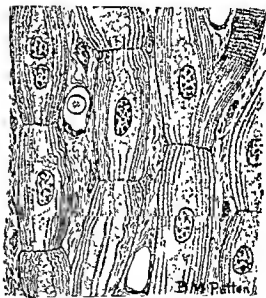
A Sinoatrial node



B. Atrioventricular node



C. Ventricular muscle



D. Purkinje fibers

Figure III-28. Drawings (X 600) showing the characteristic histology of various parts of the sinoventricular conduction system.

A. Sinoatrial node (partly after Blair and Davies, 1935). A portion of the wall of the small artery that characteristically lies in the nodal tissue is included, lower left. Note the slender strands of nodal muscle in its adventitia.

B. Atrioventricular node (partly after Blair and Davies, 1935). Note the strikingly irregular arrangement of the myofibrils at some points of branching of the fibers. This is suggestive of conditions seen in early stages of histogenesis of cardiac muscle. (Cf. Figure II-6B.)

C. Typical ventricular muscle, drawn to the same scale for comparison.

D. Fibers of the so-called Purkinje type. These are found in their most characteristic form in the terminal ramifications of the conduction bundles close under the ventricular endocardium. Where Purkinje fibers diverge from the edges of a branch, their direct continuity with typical ventricular muscle may frequently be seen (upper right).

and emerge from the node to form a single fascicle known as the atrioventricular bundle (bundle of His). This bundle pierces the right fibrous triangle (Figure III-19), courses along the caudal edge of the septum membranaceum (Figure III-26), and thus comes to lie along the apical edge of the muscular portion of the interventricular septum (Figures III-11 and III-22). This bundle of atypical myocardial fibers is somewhat isolated from adjacent cardiac muscle fibers by an investment of connective tissue. According to Mahaim (1931) and Davies and Blair (1935), the fibers of the atrioventricular bundle have essentially the same histologic characteristics as those which form the atrioventricular node (Figure III-28), except that they are arranged more nearly parallel. In some persons, however, there may be found in this bundle, fibers of considerably greater diameter which strikingly resemble the Purkinje fibers typically found more distally in the conduction system.

The Left Branches of the Atrioventricular Bundle. At the apical edge of the septum membranaceum, the bundle of His is usually described as dividing into two branches which distribute to the right and the left ventricles. This division, however, is not dichotomous (Kistin, 1949). The left branch might better be described as a broad sheet of fascicles that sweep down over the left side of the interventricular septum, immediately beneath the endocardium, to reach the papillary muscles and lateral walls of that ventricle (Figure III-27). According to Mahaim (1931), the first of these fascicles of the "left branch" may leave the bundle of His within a few millimeters of the atrioventricular node.

The Right Branch of the Atrioventricular Bundle. The right branch is usually described as single, although some instances have been reported of an accessory fascicle leaving the bundle of His to distribute fibers along the more caudal side of the interventricular septum. Ordinarily the main right branch continues the general course of the bundle of His. It may even be described as a continuation of that bundle after it has given off the last fascicle to the left. For descriptive purposes the right branch of the atrioventricular

bundle may be divided roughly into thirds. Its proximal third courses superficially, directly beneath the endocardium, to the region of the crista supraventricularis where it loses its superficial position and plunges deep within the myocardium. The middle third may be regarded as beginning at this point and ending where the branch regains its subendocardial position (Figure III-26). Its distal third is entirely superficial in position and fans out as branches to the anterior papillary muscle and to the rest of the right ventricular wall. When a moderator band is present, one of these fascicles of conduction tissue from the right branch lies within it (Truex and Copenhaver, 1947). Small fascicles from the bundle of His as well as from its two branches supply the musculature of the interventricular septum.

The fibers making up the proximal third of the right branch of the atrioventricular bundle usually have the same histologic characteristics as those making up the bundle itself. The middle third, which lies deep within the myocardium of the interventricular septum (Figure III-26), is very small in diameter and its fibers are so similar to those of the adjacent cardiac muscle that it is next to impossible to identify it by its histologic character alone. When, in its distal third, the right branch regains its subendocardial position, it branches into broad fascicles whose fibers have characteristics which justify calling them Purkinje fibers.

Purkinje Fibers. The fibers making up the left branches of the bundle of His and those of the terminal part of the right branch are about 18 micra in diameter. They have, to a certain extent, the characteristics described by Purkinje (1845) for some of the myocardial fibers in the subendocardial layer of the ventricles of ungulate hearts and, therefore, are called Purkinje fibers. Since they are rich in sarcoplasm they stain lightly. They contain relatively few myofibrilli which tend to be peripherally arranged. The striations of these sparsely distributed myofibrilli give the Purkinje fibers a weakly cross-striated appearance. The intercalated disks are readily recognizable, and between them the fibers tend to

bulge, so that they have a somewhat bloated appearance (Figure III-28). They usually contain more glycogen than do the typical cardiac muscle fibers, although this cannot be demonstrated unless the autopsy material is exceptionally fresh.

The Purkinje fibers may be seen to spread in fascicles over the subendocardial layer of the ventricles. It is not difficult to trace direct continuity between them and deeper-lying fibers of the typical ventricular myocardium. It seems reasonable that this direct continuity is the usual method of connection between the sinoventricular conduction system and the ventricular myocardium.

For the sake of clarity, the use of the designation "Purkinje fiber" should be confined to this particular type of large, pale fiber. Much of the confusion that has arisen in discussions of the sinoventricular conduction system has been caused by the indiscriminate use of the term "Purkinje tissue" to designate other parts of the sinoventricular conduction system to which it is not applicable, either historically or histologically. For similar reasons, the term "Purkinje system" should not be used to designate the sinoventricular conduction system as a whole.

An additional reason for restricting the term

"Purkinje fibers" to a purely morphologic frame of reference is that one finds this peculiar type of fiber in regions of the myocardium where it bears no apparent relationship to the sinoventricular conduction system as it is currently understood. For example, a striking percentage of the myocardial fibers of the auricles may have the morphology of Purkinje fibers (Figure III-23). In addition, one can find in the myocardium of the adult human heart, fibers that, in terms of diameter, vacuolization, and peripheral arrangement of myofibrilli, form essentially a complete spectrum between "Purkinje fibers" and "typical" cardiac muscle fibers.

In view of the variability between individuals with respect to the types of fibers making up the sinoventricular conduction system, and the occurrence of Purkinje fibers in such locations as the auricles, it is clear that much remains to be learned concerning the functional aspects of these atypical muscle fibers. At the present time we are not in a position to correlate the known functional properties of the conduction system with specific physiologic properties of the histologically distinguishable types of myocardial fibers of which it is comprised.

INNERVATION OF THE HEART

The heart receives a dual innervation from the sympathetic (thoracolumbar) and parasympathetic (craniosacral) divisions of the autonomic nervous system. The preganglionic neurons of the sympathetic division are situated in the upper five or six thoracic levels of the spinal cord. These synapse with second-order neurons which lie in the ganglia of the sympathetic trunks (White, 1936). The precise termination of the postganglionic fibers on the heart is not definitely understood.

The preganglionic neurons of the parasympathetic nervous system lie in the dorsal efferent nucleus of the medulla. Their fibers pass as branches of the vagus nerve to the heart wall, where they synapse with the second-order neurons. The latter collectively constitute a diffuse terminal ganglion. The

gross arrangement of the sympathetic (postganglionic) nerves and the parasympathetic (preganglionic) nerves to the heart is shown in Figure III-29.

The superior and middle cervical ganglia give off, respectively, the *superior* and *middle cardiac nerves*, while the *inferior cardiac nerve* arises from the inferior cervical and perhaps the first thoracic ganglion. These cardiac nerves descend to the region of the ascending aorta and arch of the aorta, around which they anastomose to form the *cardiac plexus*. Each vagus nerve contributes to the cardiac plexus by way of the *superior* and *inferior cervical nerves* and a *thoracic cardiac branch*, the latter usually arising from the recurrent laryngeal nerve.

The cardiac plexus may be divided, for de-

scriptive purposes, into a superficial and a deep portion. The *superficial cardiac plexus* is spread over the ventro-caudal surface of the arch of the aorta. It is formed chiefly by the inferior cervical cardiac branch of the left vagus nerve, and the left superior cardiac nerve of the sympathetic system. The small *cardiac ganglion* (of Wrisberg), when present, is associated with this plexus. It lies between the arch of the aorta and the pulmonary trunk, to the right of the ligamentum arteriosum (Figure III-29).

The *deep cardiac plexus* lies dorsal to the arch of the aorta, between it and the bifurcation of the trachea. It is formed by the three sympathetic cardiac nerves on the right, the three cardiac branches of the right vagus, the superior cervical and the thoracic cardiac branches of the left vagus nerve, the middle and inferior cardiac nerves of the sympathetic trunk, and direct branches from the first five or six thoracic sympathetic ganglia.

There are extensions of the cardiac plexus over the atria, especially in the region of the

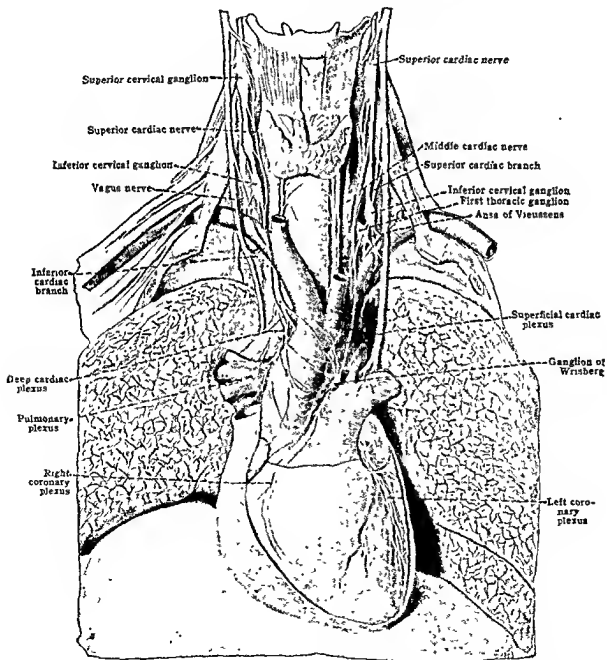


Figure III-29. Ventral view of dissection to show the nerve supply to the heart. (After Tandler, from Morris' *Human Anatomy*, courtesy of Julius Springer and The Blakiston Company.)

sinoatrial node. Ramifications from it also are present in the atrioventricular sulcus, extending along the course of the right and left coronary arteries to form the *right and left coronary plexuses*. Scattered among these nerve fibers are ganglion cells which are believed to constitute the diffuse terminal ganglion of the vagus nerve.

The nodes and bundles of the sinoventricular conduction system are accompanied by numerous nerve fibers. However, the present consensus is that the function of the autono-

mic nervous system, with regard to the heart muscle, is regulatory. Insofar as they affect the heart rate, the sympathetic fibers accelerate, and the parasympathetic fibers slow the inherent rate of rhythmicity.

There are afferent nerve fibers passing from the heart to the central nervous system, passing back along the course of the branches of the vagus and sympathetic already described, with the exception of the superior cardiac nerves of the sympathetic division (Hirsch and Orme, 1947).

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The Conduction System

MAURICE LEV

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THERE IS NOW sufficient evidence to indicate that conduction in the mammalian heart is myogenic (Davies *et al.*, 1952, Patten, 1956), although dissenting voices are still heard (Glomset and Glomset, 1940a, b, Glomset and Birge, 1945, Field, 1951b; Rossi, 1955). The exact manner of conduction, however, is only partly known. It is generally accepted that the impulse for conduction originates in the sinoatrial node, is transported through the atrial musculature to the atrioventricular node and from there proceeds through the atrioventricular bundle, the bundle branches,

and the peripheral Purkinje ramifications into the ventricular myocardium. The various structures possibly involved in this conduction system will be discussed from the standpoint of anatomy in the human heart, comparative anatomy and physiology in the mammalian heart, and pathology in the human heart. This varied discussion is necessary since many of the concepts in man are derived from the conduction system of other species. In order to aid in understanding the trodden as well as the untrodden paths, we shall introduce the discussion with a brief historical note.

HISTORICAL PERSPECTIVE

The method of initiation and propagation of the impulse in the mammalian heart has been subject to controversy for several centuries. Two schools of thought, the neurogenic and the myogenic, developed in the 19th century. The neurogenic theory gained credence earlier with the discovery of the ganglia

of Remak, Ludwig and Bidder in the frog's heart, but Gaskell (1883), McWilliam (1885), and Engelmann (1897) appeared to have established that conduction in poikilothermic animals is myogenic. However, the myogenic theory appeared inadequate when applied to birds and mammals, since no muscular con-

nections were known to exist between atria and ventricles in these classes of animals. This difficulty was overcome when His (1893) and Kent (1893) independently described such connections. In 1906, Tawara hypothesized the existence of a conduction system consisting of the atrioventricular node, bundle, bundle branches and the previously well known Purkinje fibers. Finally, in 1907, Keith and Flack described the sinoatrial node, and suggested that this was the pacemaker of the mammalian heart.

Early in the 20th century intense physiologic studies were made to test the myogenic theory in mammals and the function of the component parts of the so-called conduction system. The work, especially by Erlanger (1906), Eyster and Meek (1921) and Lewis (1925) favored the myogenic theory, and the work of Lewis and of Eyster and Meek led to the concept of conduction that is presently entertained. A modified concept of myogenic conduction by Rylant (1931), however, still remains to be evaluated. At the same time, investigation into the pathology of the con-

duction system was inaugurated, especially by Tawara (1906) and Monckeberg (1908), and led to the elucidation of the concept of heart block and the Adams-Stokes syndrome. Embryologic investigation likewise kept pace with developments in other fields (Mall, 1912; Tandler, 1913; Stiénon, 1925; Shaner, 1929-30; Sanabria, 1936; Walls, 1947; Patten, 1949; Field, 1951a; Muir, 1954). Comparative anatomists also tried to evaluate a possible conduction system in poikilothermic vertebrates (Keith and Flack, 1907; Davies, 1942).

Despite this progress in many fields, especially in electrocardiography, equal strides have not been made in the knowledge of the pathology of the conduction system. In the older literature, only Géraudel (1925), Mahaim (1931), and Yater and his associates (1936) tried to correlate electrocardiographic findings with comprehensive histologic studies of the conduction system. Since the advent of unipolar electrocardiography, Lenègre (1955) has made such correlations in a large series of cases, while several other workers have done so in only few instances.

ANATOMY IN HUMAN HEART

Sinoatrial Node (Keith and Flack, 1907; Blair and Davies, 1934-35; Glomset and Glomset, 1940a; Stotler and McMahon, 1947; Robb *et al.*, 1948; Copenhagen and Truex, 1952; Lev and Watne, 1954). The sinoatrial node lies in the sulcus terminalis, between the superior vena cava and the right atrial appendage (auricle). It extends from the recess of the right auricle to the insertion of Wenckebach's bundle (intercaval band), and lies on, and lateral to, the posterior crest. It consists of a head, body and tail. The large upper part is the head which in its thickest portion extends from epicardium to endocardium. The body tapers downward to a fine cord (tail) which lies adjacent to Wenckebach's bundle. The node is grossly not dissectable because of the large amount of collagenous and elastic tissue in its interstitial milieu which blends with similar surrounding tissue.

Histologically, the structure is easily identifiable even under low magnification (Figure

IV-1). The sinoatrial node of the adult person consists of a mass of fusiform muscle cells arranged in a plexiform manner, with a tendency of the fibers to be oriented longitudinally except for those fibers which are serpinously arranged around the artery that is constantly present. The fibers are more slender than the atrial fibers, in persons of all ages, and the nuclei are of slightly smaller diameter (Figure IV-2a). The fibers possess a relatively scant number of myofibrils with cross-striations that are less prominent than those of the typical atrial muscle. No distinct intercalated disks are in evidence. These nodal fibers are enveloped by a mass of collagenous and elastic fibers which, in persons of all ages, are more copious than those of the atrial musculature (Figure IV-2b). The reticular pattern consists of a fine mesh of lightly stained fibers which is in contrast to the coarser network of darker stained reticular fibers enveloping the atrial myocardium. Nerve cells and fibers are evi-

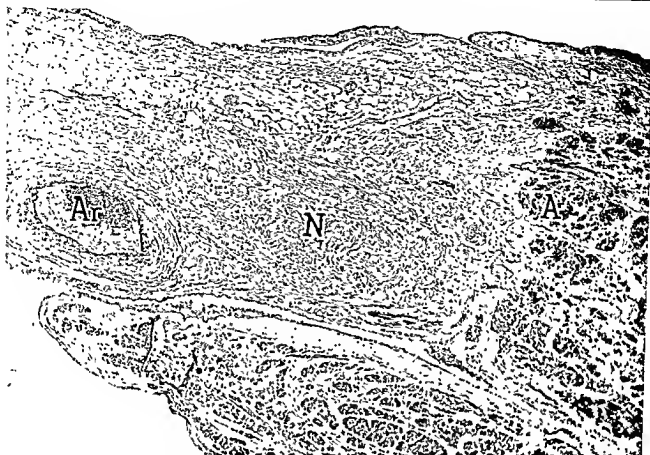


Figure IV-1. Transverse section through sinoatrial node of man. Hematoxylin and eosin. X50. A, Atrial musculature, Ar, arterial branch to node, N, node.

dent in the periphery, and nerve fibers are present in the midst of the head. The nodal muscle fibers make connections with the musculature of the superior vena cava, the confluence of the right anterior and posterior crests and the interatrial band, the posterior crest, the intercaval band and the right atrial appendage. These connections occur without the intervention of Purkinje cells. The atrial musculature connecting the sinoatrial and atrioventricular nodes shows no specific characteristics.

With advancing age, the node grows more slowly than the atrial myocardium (Lev, 1954). The collagenous fibers increase up to about the age of 40 and scarcely thereafter; the elastic tissue increases throughout life, and the reticulum fibers increase in number and coarseness. After the age of 40, apparently some muscle fibers are lost and fat is infiltrated about, and in, the node.

Atrioventricular Node, Bundle and Bundle Branches (His, 1893; Kent, 1893; Keith and

Flack, 1906; Tawara, 1906; Mönckeberg, 1908; Curran, 1909; Lhamon, 1912; Gross, 1921; Pace, 1924; Todd, 1928; Kung and Mobitz, 1930; Yater *et al.*, 1930; Mahaim, 1931; Blair and Davies, 1934-35; Robb *et al.*, 1937; Glomset and Glomset, 1940b; Walls, 1945; Truex and Copenhagen, 1947; Robb *et al.*, 1948; Kistlin, 1949; Lev *et al.*, 1951; Truex and Schwartz, 1951; Widran and Lev, 1951; Rossi, 1955). The atrioventricular node lies in the infero-distal part of the floor of the right atrium adjacent to the base of the atrial septum, between the entry of the coronary sinus and the medial leaflet of the tricuspid valve. It lies slightly below, or adjacent to, the *central fibrous body* (*trigonum fibrosum dexter*) (Figure IV-3), and its fibers are continuous with the musculature of the coronary sinus and that of the left and right atria. Grossly, it is lighter in color than that of the surrounding myocardium. It penetrates the central fibrous body to form the penetrating portion of the atrioventricular bundle (*bundle of*

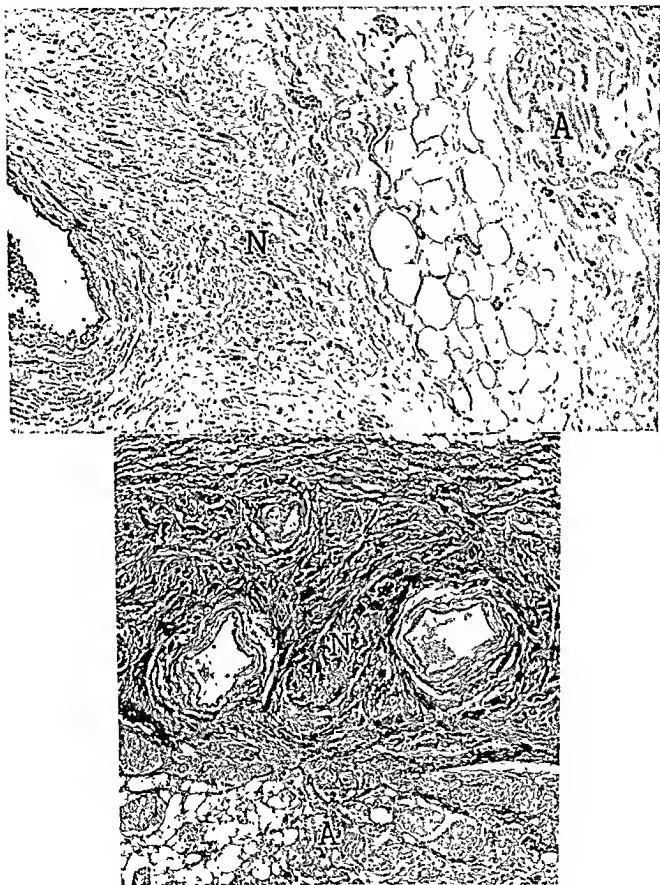


Figure IV-2. Upper. Transverse section through SA node of a 65-year-old man. Hematoxylin and eosin. X185. A, Atrial musculature; N, node.

Lower. Transverse section through the SA node to show elastic and collagenous fibers. Weigert's elastica and van Gieson. X50. A, Atrial musculature; N, node.

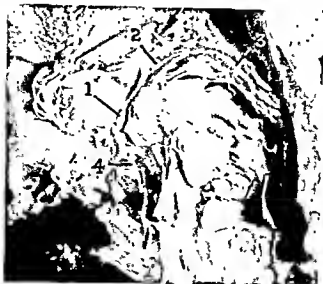


Figure IV-3. Dissection of the AV node, bundle and right bundle branch 1, AV node, 2, AV bundle; 3, right bundle branch, 4, ramus septi fibrosi.

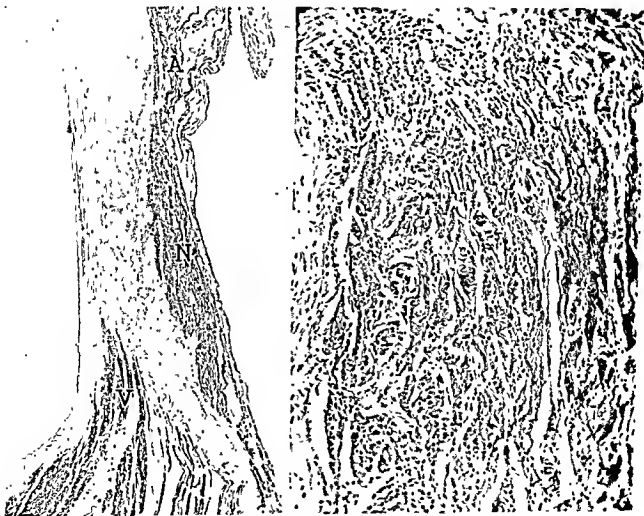


Figure IV-4. Oblique section through AV node. Hematoxylin and eosin. Left, N 15 A, Atrial musculature, N, AV node; V, musculature of ventricular septum. Right, N 90.

His). The penetrating portion then emerges from the central fibrous body to enter the lower confines of the pars membranacea where it proceeds to its distal angle. The bundle of His begins to give off the posterior radiation of the *left bundle branch* at about the point where it emerges from the central fibrous body. This radiation consists of individual fine fasciculi. The atrioventricular bundle at the distal angle of the pars membranacea bifurcates into the *right bundle branch* and the anterior radiation of the left bundle branch, the latter likewise consisting of a stream of fine fasciculi. The right branch in contrast consists of a distinct cord which proceeds along the lower margin of the septal band of the crista supraventricularis to the moderator band. In its journey, it lies below the *muscle of Lancisi* (or *Luschka*), and is usually divided into three parts. The first and third parts are subendocardial and the second part usually intramyocardial. In the region of

the anterolateral papillary muscle, the right branch divides into three terminal branches which are continuous with Purkinje networks on the inferior and anterior walls and the lower septal surface. The left bundle branch, as indicated, consists of anterior and posterior radiations of fine fasciculi which fan out beneath the endocardium and become continuous with the Purkinje network. The latter terminates in the myocardium of the anterior and posterior papillary muscles, respectively, in addition to the adjacent and the more apical myocardium. The atrioventricular node, bundle and part of the bundle branches are dissectable with scalpel or under the dissecting microscope (Keith and Flack, 1906; Tawara, 1906; Curran, 1909; Mahaim, 1931; Walls, 1945; Kistin, 1949; Widran and Lev, 1951).

The atrioventricular node, bundle and bundle branches are histologically easily identifiable. The atrioventricular node con-

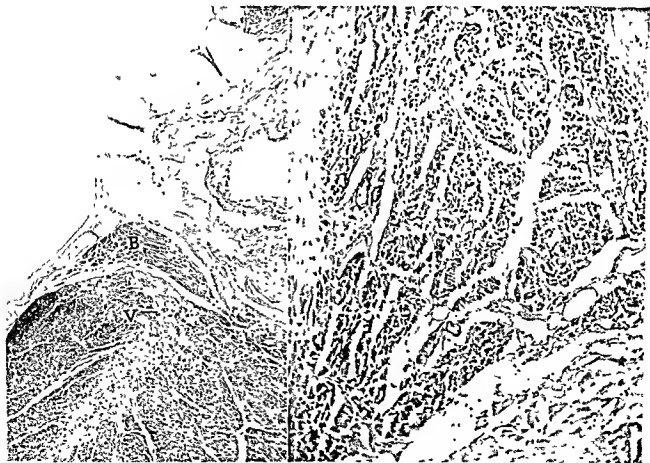


Figure IV-5. Penetrating portion of AV bundle. Hematoxylin and eosin. Left, X 15. B, Bundle, V, muscular structure of ventricular septum. Right, X 160.

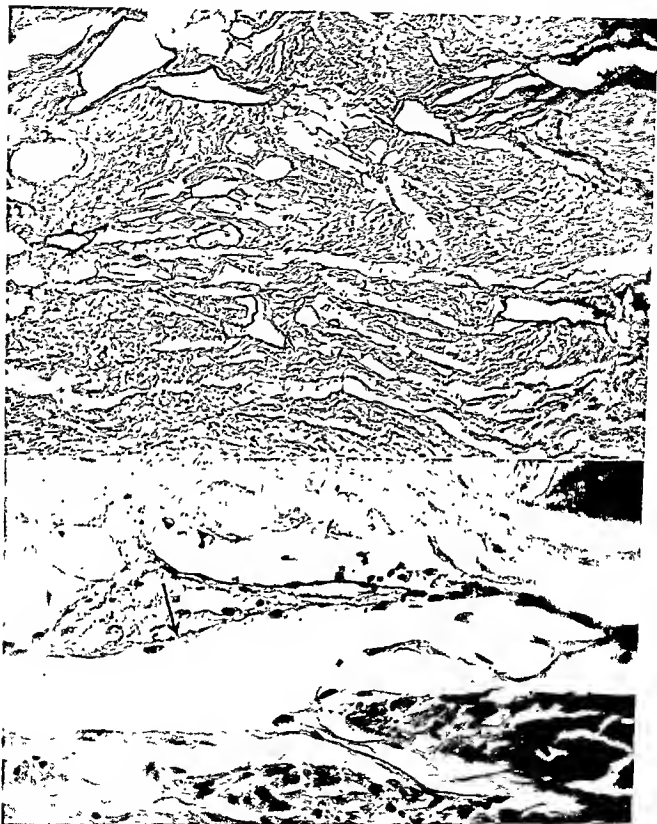


Figure IV-6. *Upper* Section of AV node, showing elastic and collagen network. Elastica and van Gieson. X 160. *Lower*. Section of sheath and enclosed space which surrounds bundle and part of bundle branches. Hematoxylin and eosin. X 810. Arrow points to the endothelium-lined sheath and space.

sists of a network of muscle fibers which are smaller than the atrial and, of course, the ventricular fibers (Figure IV-4). The cytoplasm of the nodal muscle fibers is pale in comparison to the ventricular myocardium owing to a lesser number of myofibrils. Striations are in evidence as are intercalated disks. In longitudinal plane the nuclei are oval, they do not usually show the rectangular forms of the ventricular myocardium. The node is markedly cellular because of numerous endothelial-like cells which interdigitate with the muscle cells, in some cases enclosing small spaces. In persons of all age groups, there is a greater amount of elastic fibers in the node than in the myocardium. The reticular network presents a more delicate pattern than that of the atrial or ventricular myocardium. As the fibers of the node extend to become the bundle of His, they are less plexiform and more longitudinally oriented.

The atrioventricular bundle consists of small longitudinally oriented fasciculi with cross communications (Figure IV-5). The muscle fibers are smaller than those of the ventricular myocardium, and stain more lightly owing to lesser concentration of striated myofibrils. The nuclei are smaller than those of the ventricular myocardium. A greater amount of elastic fibers is present in the bundle than in the ventricle (Figure IV-6a). The reticular structure likewise differs from that of the ventricle because of the smaller cells and the lobulated arrangement. Endothelial-like cells, similar to those around and in the node, are also found around and in the bundle where they form a distinct sheath lining a space. This sheath-lined space surrounds the right and left bundle branches (Figure IV-6b) for a varying distance distally (Curran, 1909; Lhamon, 1912).

The fibers of the left bundle branch at their origin are of the same size as those of the bundle (Figure IV-7a). However, as they proceed distally, they rapidly increase in size until they become larger than those of the ventricular musculature (Figure IV-7b). These large cells are pale with relatively few myofibrils distributed at the periphery. The nuclei are round or oval, and some cells con-

tain more than one nucleus. Although they are not identical with the Purkinje cells in sheep, we shall call them Purkinje cells. The left bundle branch and its Purkinje network show a greater amount of elastic fibers than the ventricular myocardium. Their reticular and glycoprotein basement membranes are likewise thicker.

The fibers of the right bundle branch at their origin resemble those of the bundle (Figure IV-7a). As they become intramyocardial, the fibers become larger and more or less resemble those of the myocardium (Figure IV-7c). In the third portion, the fibers are larger and resemble Purkinje cells. A greater amount of elastic fibers is present in the right bundle branch than in the myocardium.



Figure IV-7a. Section of bifurcation of AV bundle into right bundle branch and part of anterior radiation of the left bundle branch. Hematoxylin and eosin. X20. B, Bundle; L, left bundle branch; R, right bundle branch; V musculature of ventricular septum, showing considerable fibrosis.

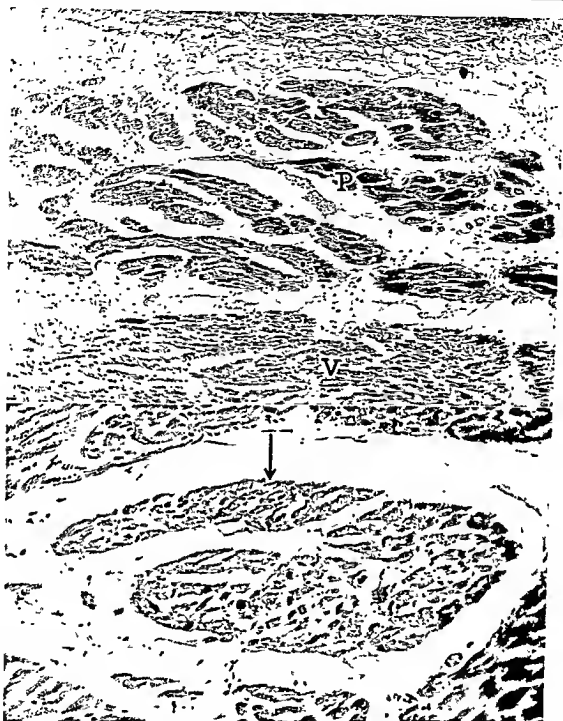


Figure IV-7b (upper). Section of Purkinje fibers in left bundle branch. Hematoxylin and eosin. X 100. P, Purkinje fibers, V, ventricular musculature.

c (lower). Section of intramyocardial portion of right bundle branch. Hematoxylin and eosin. X 180. Arrow points to right bundle branch.

The right and left bundle branches terminate in the subendocardial Purkinje network. Purkinje fibers are not present subendocardially in the conus, and in the most basilar part of the inferior, septal, anterior and lateral walls of the left ventricle (Monckeberg, 1908). The Purkinje fibers

gradually become myocardial fibers. There is no unanimity of opinion as to whether Purkinje fibers are present in the myocardium, as distinguished from the subendocardial network (Todd, 1928; Robb *et al.*, 1937; Glomset and Glomset, 1940b; Davies, 1942; Rossi, 1955).

It has recently been shown that the conduction system in man contains certain cholinesterases which are not found in the remainder of the myocardium (Carbonell, 1956). It is not certain whether the glycogen content of the conduction system differs from that of the myocardium (Yater *et al.*, 1930).

Nerve Cells are present around the atrioventricular node, but there are no nerve cells within the atrioventricular node, bundle and bundle branches (Blair and Davies, 1934-35, Glomset and Glomset, 1940a, b, Glomset and Birge, 1945, Stotler and McMahon, 1947; Field, 1951b; Glomset and Gross, 1952, Rossi, 1955). Nerve fibers are present in the atrioventricular node and bundle, and to a lesser extent in the upper part of the bundle branches. No nerve fibers are present in the lower parts of the bundle branches or in the peripheral Purkinje network.

The Blood Supply of the sinoatrial node is by way of the ramus ostii cavae superioris (Gross, 1921). This vessel arises from the beginning of the right main coronary artery in about 90 per cent of hearts, and from the left circumflex coronary artery in the remainder. The blood supply to the atrioventricular node and bundle is by way of the ramus septi fibrosi (Gross, 1921, Mahaim, 1931; Lascano, 1943) which arises from the main right coronary artery just before it gives off the posterior descending branch in about 90 per cent of instances, and from the left coronary artery when it forms the posterior descending artery. The first part of the right bundle branch is supplied by the ramus septi fibrosi, the ramus septi ventriculorum superior, and the ramus cristae, all coming from the right coronary artery, and the first anterior perforating vessel from the left anterior descending. The second part of the right bundle branch is supplied by



Figure IV-8 Section through muscular connections between terminal portion of AV node and musculature of ventricular septum, van Gieson. X 135. Arrows point to the connections. N, Node, V, musculature of ventricular septum. Dark stained areas denote connective tissue pierced by the muscular connections.



Figure IV-9. Section of muscular connections between AV bundle (B) and musculature (V) of ventricular septum in an adult, cut at different levels. *a* (left). Weigert's elastica and van Gieson. X 45. *b* (right). Hematoxylin and eosin. X 45. Arrows point to the connections.

the ramus limbi dextri coming from a branch of the left anterior descending, and the anterior and posterior perforating arteries coming from both the anterior and posterior descending arteries. The most distal part of the right bundle branch is supplied by branches from both the right and left coronary arteries supplying the adjacent myocardium. The first part of the left bundle branch is supplied by the ramus septi fibrosi, the ramus septi ventriculorum superior, and the ramus cristae, all from the right coronary artery, and the ramus limbi sinistri from the anterior descending. The second portion is supplied by the anterior and posterior perforating vessels from both the right and left coronaries, and the third portion from the same group of vessels supplying the surrounding myocardium.

The atrioventricular node, bundle and bundle branches, like the sinoatrial node, have a different aging cycle than the remainder of the myocardium (Mönckeberg, 1908; Bon-dolini, 1937; Erickson and Lev, 1952). These structures are relatively larger in fetal life and childhood than in later life. With advancing age, there is an increase in collagenous and elastic tissue, an increase in density of reticulum in all structures, and an infiltration of

fat in the atrioventricular node, bundle and beginning of the right bundle branch. In contrast, the ventricular myocardium shows only a small increase in elastic and collagenous tissue with advancing age.

Mahaim's Paraspecific Fibers (Mahaim and Winston, 1941; Lev and Lerner, 1955). In the fetus and at birth, small groups of muscle fibers connect the distal part of the atrioventricular node (Figure IV-8), the atrioventricular bundle (Figure IV-9) and the beginning of the left bundle branch with the upper part of the muscular ventricular septum (Figure IV-10). These are perhaps less numerous in adult life but such small connections may be found, especially between the atrioventricular bundle and the beginning of the left bundle branch and the ventricular septum. No such connections are present between the right bundle branch and the upper part of the septum in man.

Kent's Fibers (Kent 1893, 1913). It is questioned whether muscular fibers normally connect the atria and ventricles outside the confines of the atrioventricular node, bundle and bundle branches, as stated by Kent. Such connections do not appear to be present in the majority of normal hearts (Lev and Lerner, 1955).

COMPARATIVE ANATOMY IN MAMMALIAN HEART

The sinoatrial and atrioventricular nodes of all mammals, including man, are similar. However, there is a marked difference between the atrioventricular bundle and bundle branches and their nerve supply in ruminants, pig and horse on the one hand, and in man, monkey, dog, cat, rat, rabbit and guinea pig on the other. The conduction systems of the monotreme and the hamster have unusual features.

Ruminants (sheep, cattle) (Tawara, 1906, Keith and Flack, 1907; King, 1916, Jordan and Banks, 1917, Pace, 1924; Scaglia, 1927; Todd, 1928; Shaner, 1929-30, Blair and Davies, 1934-35; Abramson and Margolin, 1935-36, Sanabria, 1936, Vitali, 1937, Glomset and Glomset, 1940a, b; Mahaim and Winston, 1941; Truex and Copenhaver, 1947; Field, 1951a; Copenhaver and Truex, 1952, Davies

and Francis, 1952; Davies *et al.*, 1952). The sinoatrial node in the sheep is similar to that in man and consists of a horseshoe-shaped structure lying in the sulcus terminalis. Histologically, this consists of a network of small cells, smaller than the atrial fibers, which lie in a sea of connective tissue. These cells contain elongated nuclei and fewer striated myofibrils than those of the myocardium, and exhibit rare intercalated disks. Nerve cells are present only in the periphery, but nerve fibers are present within the node itself. The sinoatrial node is directly continuous with the surrounding myocardium. The atrioventricular node consists of an irregular network of small fibers with oval nuclei, and few myofibrils with scant striations. According to Tawara (1906), this is continuous with a more proximal network of ordinary atrial



Figure IV-10. Section of muscular connection between the beginning of left bundle branch and musculature of ventricular septum. Hematoxylin and eosin. X45. Arrow points to the connection. L, Left bundle branch, V, musculature of ventricular septum.

fibers which in turn connects with the atrial myocardium. The atrioventricular node is continuous with the atrioventricular bundle in the fibrocartilaginous septum. The atrioventricular bundle consists of large Purkinje-like cells which are larger than the ventricular myocardial fibers. The atrioventricular bundle bifurcates into left and right branches. The cells of the left branch rapidly enlarge to become classical Purkinje cells. In the right branch, the change to Purkinje cells is more gradual. These cells are not only subendocardial, but also intramyocardial, and gradually become continuous with myocardial cells. A sheath, enclosing a distinct space, surrounds and interdigitates with the bundle, the bundle branches, and the terminal Purkinje fibers up to their termination in the myocardium. The atrioventricular node, bundle and bundle branches and Purkinje arborizations all contain ganglion cells and nerve fibers. There is no connection, however, between the nerve fibers about the Purkinje cells and the myocardium itself. Paraspecific fibers pass from the atrioventricular bundle and left bundle branch to the ventricular myocardium (Mahaim and Winston, 1941).

The classical Purkinje cells as seen in the bundle branches of the sheep are very large, much larger than the ventricular myocardial fibers (Todd, 1928; Abramson and Margolin, 1935-36; Truex and Copenhaver, 1947; Davies and Francis, 1952). The central region of the cell is unstained, contains one to three nuclei, and is surrounded by a granular zone. Few myofibrils are present in the periphery of the cells which have rather faint transverse striations. The sarcoplasm, according to some, is rich in glycogen and rarely has fat inclusions. Granular mitochondria are situated between the myofibrils and around the nucleus (Santana, 1936).

The sinoatrial node of cattle resembles that of sheep. However, it consists of a bead in addition to the horseshoe-shaped portion. According to Blair and Davies (1934-35), the node has, not only small cells but also, large Purkinje-like cells. The node joins the atrial myocardium directly and also by way of

Purkinje cells. The atrioventricular node, bundle and bundle branches resemble those of the sheep in general morphology and in their contained nerves (Tawara, 1906; Scaglia, 1927; Blair and Davies, 1934-35; Vitali, 1937; Davies *et al.*, 1952).

Hog and Horse. In general, the conduction system of the hog resembles that of sheep and cattle (Abramson and Margolin, 1935-36; Glomset and Glomset, 1940a,b; Truex and Copenhaver, 1947; Davies *et al.*, 1952). The atrioventricular node, however, lies nearer the base of the tricuspid valve. Likewise, although nerve fibers are present throughout the system, nerve cells are not present in the bundle and bundle branches. In general, the conduction system of the horse resembles that of the hog (Keith and Flack, 1906; Davies and Francis, 1952; Davies *et al.*, 1952).

Dog and Cat. The sinoatrial node of the dog is similar to that of other mammals (Tawara, 1906; Abramson and Margolin, 1935-36; Mahaim and Winston, 1941; Nonidez, 1943; Baird and Robb, 1950; Field, 1951b; Tcheng, 1951; Truex and Schwartz, 1951; Davies and Francis, 1952; Davies *et al.*, 1952). It extends from the angle formed by the superior vena cava and the atrial appendage (auricle) to the angle of junction of the superior vena cava and the inferior vena cava. It is club-shaped and tapers to a fine end. The atrioventricular node resembles that found in other mammals. It contains not only small cells but larger Purkinje-like cells. The atrioventricular bundle, like the node, consists of small cells. According to Baird and Robb (1950), it passes entirely unsheathed through the lower part of the membranous septum. Only distal to this point is a sheath present, with a small space, as in man.

The cells at the beginning of the left bundle branch and right bundle branch resemble those of the bundle. More distally, sooner in the left than in the right bundle branch, the fibers enlarge somewhat and have some of the characteristics of the Purkinje cells of the sheep, being larger than the myocardial fibers but never attaining the marked differentiation found in the sheep. Opinions differ as to

whether these Purkinje-like cells penetrate into the myocardium (Tawara, 1906; Abramson and Margolin, 1935-36; Davies, 1942). Paraspecific fibers are present from the atrioventricular bundle and left bundle branch (Mahaim and Winston, 1941, Baird and Robb, 1950). The atrioventricular node, bundle and bundle branches are grossly dissectable (Baird and Robb, 1950). Ganglia are present around the atrioventricular node, but no nerve cells are present in the atrioventricular node, atrioventricular bundle and bundle branches (Nontdez, 1943; Field, 1951b, Tchong, 1951; Davies *et al.*, 1952). Many nerve fibers are present in the atrioventricular node, some in the bundle, few or none in the upper parts of the bundle branches, and none are found in the peripheral Purkinje network. The conduction system of the cat resembles that of the dog (Truex and Copenhaver, 1947; Davies *et al.*, 1952), but paraspecific fibers are present from the right bundle branch as well as from the atrioventricular bundle and the left bundle branch (Mahaim and Winston, 1941).

Rat (Tawara, 1906, Meiklejohn, 1913-14, Davies and Francis, 1952, Davies *et al.*, 1952, King, 1954, Prakash, 1954). There is a difference of opinion as to the existence of a sinoatrial node in the rat. Apparently the atrioventricular node resembles that in other mammals, and the atrioventricular bundle and bundle branches resemble those in the dog (Davies and Francis, 1952). The right bundle branch is short, however, and the left bundle branch passes deep into the muscular fibers of the ventricular septum before becoming subendocardial. Purkinje cells are present beneath the endocardium in the atria. Paraspecific fibers pass from the bundle to the ventricle. No nerve cells are found in the atrioventricular node, bundle or bundle branches. Many nerve fibers are present in the atrioventricular node, some in the bundle, few in the upper part of the bundle branches, and none in the Purkinje network (Davies *et al.*, 1952).

Golden Hamster (Walls, 1942). The sinoatrial node is horseshoe-shaped, lying in the sulcus terminalis ventral to the right superior

vena cava. The node is composed almost entirely of muscle fibers which are of two types, some smaller than the atrial and some larger ones resembling Purkinje cells. The nodal fibers have direct continuity with the atrial and sinus musculature, and no Purkinje fibers are found in the walls of the atria. The atrioventricular node consists of two parts, a more deeply placed interlacing network of fibers indistinguishable from atrial fibers from which the atrioventricular bundle arises, and a more compact subendocardial bundle many of whose cells resemble Purkinje cells. The atrioventricular bundle consists mostly of large Purkinje-like cells. The right bundle branch takes a short course and disappears into the right ventricle. No Purkinje fibers are found in this chamber. The left bundle branch is buried in the septum and becomes continuous with the myocardium. Below the level of disappearance of the left bundle branch, Purkinje fibers appear in the ventricular wall and are in continuity with the myocardial fibers. No nerve cells are present in the atrioventricular node, bundle or bundle branches. The atrioventricular node and bundle branches are poor in nerve fibers, while the bundle contains many nerve fibers.

Rabbit (Tawara, 1906; Lloyd, 1930, Sanabria, 1936, Mahaim and Winston, 1941, Field, 1951b; Davies and Francis, 1952; Davies *et al.*, 1952). The sinoatrial and atrioventricular nodes of the rabbit resemble those in other mammals, and the atrioventricular bundle and bundle branches resemble those of the dog. Paraspecific fibers join the atrioventricular node, the bundle and the right bundle branch to the ventricular musculature. There are no nerve cells in the atrioventricular node, bundle or bundle branches. Nerve fibers are present in the atrioventricular node, a lesser number in the bundle, few in the bundle branches, and none distally.

Guinea Pig (Tawara, 1906; Robb and Kaylor, 1945; Field, 1951b; Davies *et al.*, 1952). The sinoatrial and atrioventricular nodes apparently are similar to those in other mammals and the atrioventricular bundle and bundle branches resemble those of the dog. In addition, there are numerous paraspecific

fibers passing from the bundle and the right and left bundle branches to the septum. No nerve cells are found in the atrioventricular node, bundle and bundle branches. Nerve fibers are present in the node, a lesser number are noted in the bundle, few in the bundle branches, and none distally.

Monkey (Nonidez, 1943; Truex and Copenhaver, 1947; Field, 1951b; Copenhaver and Truex, 1952). The sinoatrial and atrioventricular nodes of the monkey resemble those in other mammals and the atrioventricular bundle is like that of the dog. The bundle branches consist of Purkinje-like cells which are only slightly larger and differ minimally from the myocardial fibers. There are no nerve cells in the atrioventricular node, bundle and bundle branches. Nerve fibers, however, are present in the node, bundle, and in the beginning of the bundle branches.

Monotreme (echidna, platypus) (Keith and Mackenzie, 1910, Davies, 1930-31). The sinoatrial node is relatively more massive than in placental mammals, and in echidna is very vascular. Histologically, it resembles that of placental mammals, but transverse striations have not been seen. Nerve cells are present in the node, in contrast to placental mammals. The atrioventricular node is large and resem-

bles that seen in placental mammals, but again no transverse striations are in evidence. Communications exist between the atrioventricular node and the upper part of the ventricular septum. The atrioventricular bundle is likewise large and resembles that of ruminants. The right bundle branch divides into anterior and posterior branches, all three making connection with the ventricular septal musculature proximally and distally. The left bundle branch is larger than the right and subdivides into four branches. The main branch likewise makes connections with the ventricular septum high in its course. Both the right and left bundle branches consist of Purkinje cells, and terminate in the subendocardial Purkinje network. No Purkinje network is present in the myocardium. Davies (1930-31) could not find accessory communications between the atrium and ventricle outside the conduction system previously described by Keith and Mackenzie (1910). No nerve cells are present in the atrioventricular node, bundle and bundle branches. Nerve fibers are present in the atrioventricular node, a lesser number in the atrioventricular bundle, a few in the bundle branches, but none occur distally.

COMPARATIVE PHYSIOLOGY IN MAMMALS

Since little is known about the physiology of the conduction system in man, the knowledge gained by the study of the conduction system of the dog and other laboratory animals will be utilized to explain physiologic phenomena in man.

Function of Sinoatrial Node. The function of this structure has been gleaned from effects (a) of application of heat and cold (Flack, 1910, Canter and Zahn, 1912; Zahn, 1913, Erlanger, 1913; Schlomovitz and Chase, 1917; Eyster and Meek, 1921; Davies and Francis, 1946); (b) of toxic agents (Flack, 1910, Eyster and Meek, 1921; Davies and Francis, 1946); (c) of clamping and excision (Erlanger and Blackman, 1907; Flack, 1910, Cohn and Kessel, 1911; Cohn *et al.*, 1911-12; Moorhouse, 1912; Erlanger, 1913; Eyster and Meek, 1921,

1922, Borman, 1926; Jourdan *et al.*, 1945; Davies and Francis, 1946); and from (d) electrical analysis (Lewis, 1910, 1913, 1925; Wybauw, 1911; Erlanger, 1913, Eyster and Meek, 1913-14, 1921; Eccles and Hoff, 1934; Davies and Francis, 1946). The sinoatrial node is especially sensitive to application of moderate heat which greatly accelerates the heart rate. However, other parts of the atria may also respond to increased temperatures, thereby increasing the over-all rate of the heart beat. This is taken to indicate that under normal conditions the sinoatrial node is the pacemaker. Application of cold to the sinoatrial region produces nodal or coronary sinus rhythm. Likewise, upon excision or clamping of the sinoatrial area, nodal or coronary sinus rhythm results. The clear inference

that may be drawn from the above experiments is clouded by the question of localization of the irritants, some workers contending that the tissue originating from the sinus venosus (Erlanger, 1913), and not the sinoatrial node itself, is the pacemaker.

Electrical experiments have been utilized to pinpoint the region of the pacemaker. These include localization of the point of initial negativity and determination of the contour of the wave upon galvanic stimulation. The point of initial negativity was found by Lewis (1910) to be in the cephalic portion of the sinoatrial node; Wybauw (1911) found it in the middle of the node; and Eyster and Meek (1913-14) and Eccles and Hoff (1934) found it sometimes in the cephalic and sometimes in the middle portion of the node. Galvanic stimulation shows that the normal P wave is obtained only upon stimulation of the sinoatrial node. These experiments have been taken to mean that the sinoatrial node is the pacemaker. Erlanger (1913), however, suggests that these experiments only show that the impulse enters the atria through the region of the sinoatrial node, but that the pacemaker may be that portion of the right atrium originating from the sinus venosus.

Conductive Function of Right Atrium. No specialized pathway between sinoatrial and atrioventricular nodes has been identified. The present consensus is that the impulse is conducted from the sinoatrial node to the atrioventricular node through the ordinary musculature of the right atrium. The manner of the propagation of the impulse through the atrium is controversial. According to Lewis (1917), the impulse radiates in all directions from the sinoatrial node, reaching the atrioventricular node through no set pathway. Eyster and Meek (1916, 1917) indicated that there are two alternate pathways from the sinoatrial to the atrioventricular node, the shorter route being directly to the atrioventricular node, and the longer one traversing the right atrium. According to Rylant (1931), the impulse from the sinoatrial node reaches the subendocardial portion of the atrium from which it is disseminated diffusely through the atrium before reaching the region of the coronary sinus.

Function of Atrioventricular Node and Coronary Sinus. If the sinoatrial node is rendered functionless, then the impulse is initiated either from the region of the coronary sinus or from the atrioventricular node (Flack, 1910; Cohn *et al.*, 1911-12; Ganter and Zahn, 1912; Zahn, 1913; Eyster and Meek, 1916, 1917, 1921, 1922; Davies and Francis, 1946). It appears that the tissue about the coronary sinus has a slightly greater inherent rhythmicity than the atrioventricular node (Eyster and Meek, 1917). Because of the experimental difficulties in separating the two regions, it is not clear whether a "coronary sinus rhythm" differs from the atrioventricular nodal rhythm (Clere and Pezzi, 1920; Scherf, 1944). Because of the low conductivity of the atrioventricular node, the impulse is slowed considerably in this region, accounting for most of the PR interval in the electrocardiogram.

Function of Atrioventricular Bundle, Bundle Branches, and Purkinje Network. The function of the atrioventricular bundle and bundle branches is to transmit the impulse to the ventricular myocardium. Cutting or crushing the bundle of His almost always produces partial or complete heart block (Erlanger, 1906, Biggs, 1908; Erlanger and Miller, 1909; Erlanger and Blackman, 1909-10; Cullis and Dixon, 1911; Eyster and Meek, 1921; Davies and Francis, 1946). Whether this results from cutting of the muscular communications or the nerves in the bundle is not clear. Cullis and Dixon (1911) applied cocaine to the bundle to depress the nerves but did not produce heart block in this manner. Likewise the application of nicotine, a nerve stimulant, to the bundle had no immediate effect, whereas when the bundle was depressed by chloroform or other drugs which affect muscle only, it could not be then stimulated electrically. It was thought that these experiments indicated that conduction was along the muscular and not the nerve route. Conduction through the atrioventricular bundle, bundle branches and Purkinje fibers is rapid. However, the atrioventricular bundle shows a low rate of inherent rhythmicity.

Cutting of either bundle branch in the dog causes a lag in contraction of the correspond-

ing ventricle, and complete heart block has resulted from cutting of both branches. In view of the paucity or absence of nerve fibers in the bundle branches, these findings are taken to confirm the theory of myogenic conduction (Davies *et al.*, 1952).

The role of the paraspecific fibers of Mahaim in conduction is controversial. Mahaim and Winston (1941) found that when the fibers were numerous or of larger size, cutting of the bundle branches did not produce complete block. Others have minimized their physiologic importance (Meessen, 1935).

Conductive Properties of Ventricles. The manner in which the impulse is propagated through the ventricles is not definitely known. In sheep and cattle, in which a Purkinje network is known to exist throughout the myocardium, it is agreed that the impulse passes through the Purkinje network to the myocardium. In man and the dog, there is a difference of opinion as to whether Purkinje fibers exist in the myocardium. Likewise, experimental evidence in the dog of the

method of propagation in the ventricles has been variously interpreted. According to Lewis and Rothschild (1915) and Ahramson and Jochim (1937), the impulse passes from the endocardium through the myocardium at right angles to the endocardial surface. The latter authors believe that this is through the Purkinje network first, then the myocardium. According to Robb and Robb (1936), the path of propagation is along the direction of muscle bundles of the heart. It is agreed that subendocardial propagation is much faster than that through the remainder of the myocardium. Lewis thought that this is due to the property of conduction of Purkinje fibers in the subendocardial region. According to Pruitt and associates (1951), this difference in speed of conduction is explained by the direction of fibers in the subendocardial and intramyocardial regions, conduction subendocardially being direct, and that in the myocardium being at right angles to the direction of the stimulus.

PATHOLOGY IN THE HUMAN HEART

The conduction system may be involved directly or by contiguity in all diseases affecting the heart in general. Thus, the sinoatrial and atrioventricular nodes, the bundle and the bundle branches may be involved in congenital heart disease, hypertensive and arteriosclerotic heart disease, rheumatic heart disease, syphilitic heart disease, and in endocarditis, myocarditis and pericarditis. The pathologic changes noted include granular, vacuolar and fatty degeneration, necrosis, acute and chronic inflammation, fibrosis, elastosis, hyperemia, hemorrhage, pigmentation and calcification. The sinoatrial and atrioventricular nodes and atrioventricular bundle are not subject to atrophy or hypertrophy (Aschoff, 1906; Tawara, 1906; Keith and Flack, 1907; Monckeberg, 1908). In the occasional case in which it has been investigated, amyloid has not been found (Monckeberg, 1908). No tumor is known to have originated from the muscular parenchyma of the conduction system.

Congenital Heart Disease. The atrioventricular node, bundle and bundle branches may show a primary abnormality in position, or a disruption in continuity or a secondary fibrotic replacement. In addition, accessory bundles may be present, either replacing or accompanying the normal structures.

The atrioventricular node, bundle and bundle branches have been found to be normal in subaortic ventricular septal defects (Monckeberg, 1908, 1913, 1924; Mahaim, 1931), and in patent foramen ovale. In all such ventricular septal defects, the atrioventricular bundle lies below the defect (Monckeberg, 1924; Mahaim, 1931). In patent foramen primum, the atrioventricular node is displaced posteriorly, while the bundle arises in the connective tissue below the defect, and at its distal margin divides into its bundle branches (Monckeberg, 1913, 1924; Morison, 1913) (Figure 1V-11). In cor triloculare biventriculosum, the atrioventricular node and the beginning of the bundle have a course similar

to that in persistent ostium primum (Monckeberg, 1913). In cor biatriatum triloculare (Monckeberg, 1924), the atrioventricular bundle lies on a ridge in the posterior wall representing the remnant of the posterior septum, where it divides into right and left branches. In cor biloculare (Monckeberg, 1924), the atrioventricular node originates in the median portion of the posterior atrial wall and continues as the atrioventricular bundle which takes the same course as in common ventricle. In aneurysm of the pars membranacea, the bundle may be deviated (Castoldi, 1942). In these anomalies, therefore, there may be an abnormality in position but not necessarily an abnormality in continuity.

Abnormalities in continuity between the atrioventricular node and atrioventricular bundle or within the atrioventricular bundle have been found in patent foramen primum (Monckeberg, 1913; Yater, Barrier and McNabb, 1934; Wallgren and Winblad, 1938), transposition of the atria or ventricles (Monckeberg, 1913; Yater, 1929a; Uher, 1935-36; Abbott, 1936), cor biatriatum triloculare (Wilson and Grant, 1925-26; Abbott and Mofatt, 1946), large ventricular septal defect (Perotti, 1928; Yater *et al.*, 1933; Rogers and Rudolph, 1951; Turpin *et al.*, 1947), and in cor triloculare biventriculosum (Yater, Leaman and Cornell, 1934). In cor biloculare and patent foramen primum (Monckeberg, 1913), anterior accessory atrioventricular connections may be present on the anterior atrial wall in place of the normal, and may pass into the subendocardial part of the left ventricle where the bundle branches are given off; or other accessory anterior connections may join the normal posterior connection to form a common bundle that proceeds downward into the ventricles and then divides. These abnormalities may result in congenital complete or incomplete atrioventricular block.

Congenital complete atrioventricular block is a relatively rare abnormality. In addition to the conditions described above in which studies have been made of the conduction system, congenital complete atrioventricular block has been described in tricuspid atresia (Hoekenga, 1945; Dickson and Jones, 1948;

Aitchison *et al.*, 1955) and hypoplasia of the aortic tract complex with mitral atresia (Donoso *et al.*, 1956), tetralogy of Fallot (Bernreiter and O'Connell, 1952), Eisenmenger complex (Campbell and Thorne, 1956), bicuspid aortic valve with sclerosis and calcification (Clark and Firminger, 1949), fibroelastosis (Rotem, 1950; Stadler *et al.*, 1950), fetal coarctation (Witt, 1934; Wendkos and Study, 1947), congenital aneurysm of the pars membranacea (Clark and White, 1952), and in enlarged but otherwise normally formed hearts (Plant and Stevens, 1945).

In congenital heart disease, the right and

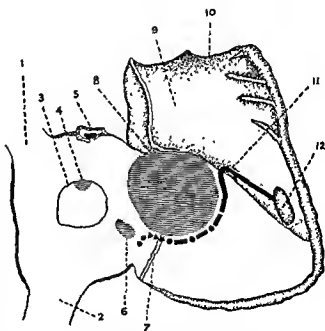


Figure IV-11. Diagrammatic sketch of right atrial and ventricular view of a heart with common atrioventricular orifice. Dark dot and dash line show the position of the AV node, AV bundle and right bundle branch.

-, AV node
- △△, Penetrating portion of AV bundle
- , Branching portion of AV bundle
- , Right bundle branch
- 1, Superior vena cava
- 2, Inferior vena cava
- 3, Limbus fossa ovalis
- 4, Patent foramen ovale
- 5, Cut edge of removed atrial appendage
- 6, Entry of coronary sinus
- 7, Base of tricuspid valve
- 8, Shaded area denoting combined patency of atrial and ventricular septa
- 9, Pulmonary conus
- 10, Base of pulmonary valve
- 11, Muscle of Lancisi
- 12, Cut edge of moderator band

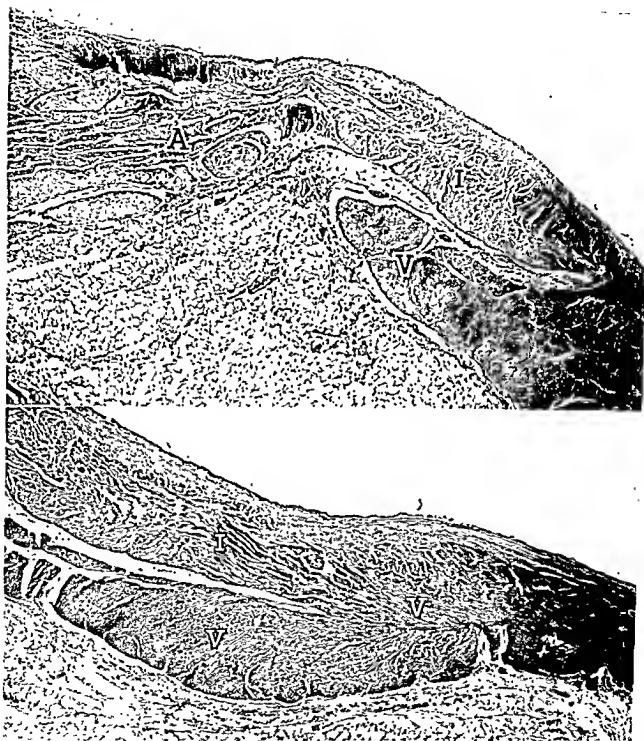


Figure IV-12. Muscular communication between parietal walls of right atrium and right ventricle in a case of Ebstein's complex. This was achieved by junction with an intermediate bundle.

Upper. Communication between intermediate bundle and atrial myocardium. van Gieson X 45. A, Atrial musculature, I, intermediate bundle, V, ventricular musculature.

Lower. Communication between intermediate bundle and ventricular myocardium, Hematoxylin and eosin. X 45 I, Intermediate bundle, V, ventricular musculature.

left bundle branches may show pathologic change. Thus, in an occasional case of sub-aortic stenosis (Lenègre *et al.*, 1945), the left bundle branch may be encased in fibrous tissue and be disrupted in continuity. In Ebstein's malformation, the right bundle branch may be so involved (Yater and Shapiro, 1937, Lev *et al.*, 1955). These findings may be associated with right or left bundle branch block. Congenital absence of the right bundle branch has been reported (Coakley, 1951) and transposition of both bundle branches occurs in transposition of the ventricles (Aschoff, 1937). The anatomic basis, however, of most cases of right bundle branch block in congenital heart disease is unknown. Abnormalities in the sinoatrial node, to date, have not been described.

Accessory bundles between atria and ventricles have been described in instances of Wolff-Parkinson-White syndrome (Lev *et al.*, 1955). These may be found between the right or left atrium and the respective ventricle. This syndrome has been found to be associated with Ebstein's malformation (Lev *et al.*, 1955) (Figure IV-12), ventricular septal defect (Segers *et al.*, 1947), coarctation of the

aorta (Bodlander, 1946), and in hearts apparently not the seat of other congenital malformations.

Hypertensive and Arteriosclerotic Heart Disease. Occlusion or narrowing of the right main coronary artery at its origin, before the origin of the ramus ostii cavae superioris, may produce ischemic changes in the sinoatrial node and the atrioventricular node and bundle, the beginning of both bundle branches and the posterior radiation of the left bundle branch (Monckeberg, 1908, Lev and Unger, 1955). Occlusion of the right main coronary artery distal to the origin of the ramus ostii cavae superioris and proximal to the origin of the ramus septi fibrosi may produce similar changes while sparing the sinoatrial node (Mahaim, 1931). Occlusion of the right main coronary artery distal to the origin of the ramus septi fibrosi may produce ischemic changes in the posterior radiation of the left bundle branch (Mahaim, 1931). Narrowing or occlusion of the anterior descending coronary artery in its first 1-2 cm., proximal to the origin of the second perforating branch, may produce ischemic changes in the mid-portion of the right bundle branch and the

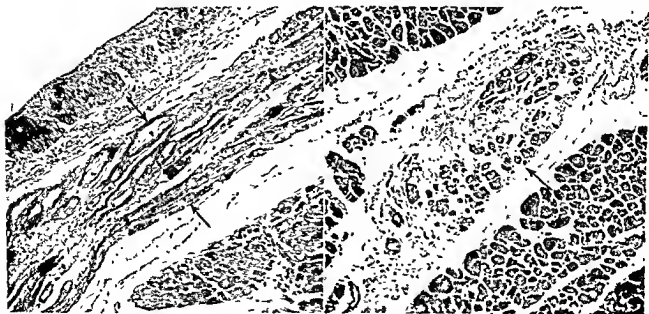


Figure IV-13 Left. Section of left bundle branch showing necrosis of fibers of left bundle branch. Note increase in depth of staining of sarcoplasm of some fibers and marked vacuolization of that of others. Also note pyknosis of some nuclei. Hematoxylin and eosin. X 150. Arrows point to the left bundle branch.

Right. Section of right bundle branch showing necrosis and fibrosis of right bundle branch. Hematoxylin and eosin. X 170. Arrows point to right bundle branch. Note irregularly increased staining of sarcoplasm of remaining fibers.

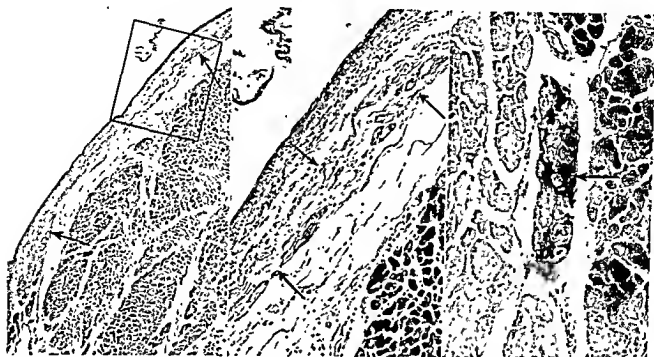


Figure IV-14 *a* (left) and *b* (middle). Section of left bundle branch showing fibrosis. Hematoxylin and eosin. *a*, X 50, *b*, X 170. Arrows point to the left bundle branch. Area enclosed in *a* denotes region magnified in *b*.

c (right). Section of right bundle branch showing fibrosis. Weigert's elastica and van Gieson. X 170. Arrow points to right bundle branch.

anterior radiation of the left bundle branch (Mahaim, 1931). Narrowing of the anterior descending artery, distal to the origin of the second anterior perforating vessel, may produce ischemic changes in the anterior radiation of the left bundle branch alone (Mahaim, 1931). The ischemic changes that may be found include necrosis, fibrosis and calcification (Figures IV-13 and 14). As in the remainder of the myocardium, ample anastomoses may form in the blood supply to the conduction system after the development of coronary sclerosis, and hence the rate of narrowing of the vessels and the age of the individual are factors in production of ischemia (Lascano, 1943). In addition, the sinusoidal arrangement of the atrioventricular node and bundle may be a sparing factor in ischemia (Truev and Schwartz, 1951). In narrowing of the large coronary arteries, the general myocardial changes dominate the scene, with or without the accompaniment of disturbances in sinoatrial and atrioventricular conduction and right and left bundle branch block (Mahaim, 1931, Yater, 1938). The

ramus septi fibrosi may be exclusively narrowed, however, leading to isolated changes in the atrioventricular node and bundle and the surrounding atrial musculature (Mahaim, 1931). In arteriosclerosis of the coronaries without narrowing of the large arteries, there may be pathologic involvement of the conduction system, usually of both the right and left bundle branches focally, leading to various types of bundle branch block (Mahaim, 1931; Yater, 1938; Lev and Unger, 1955).

A separate form of arteriosclerotic heart disease, unrelated to coronary sclerosis and narrowing, is marked sclerosis and calcification at the base of the aortic leaflet of the mitral valve involving the adjacent pars membranacea and the ventricular myocardium at its junction with the pars membranacea (Monckeberg, 1908; Mahaim, 1931; Yater and Cornell, 1935) (Figure IV-15). This common aging change, occurring usually in the seventh decade and seldom before the age of 50, may involve the atrioventricular node or bundle or the bifurcation by fibrosis and calcification; it may be associated with

infiltration of lymphoid cells. Another less common but equally important aging lesion is calcific change which involves the aortic valve at the lower margin of the sinuses of Valsalva and spreads to the pars membranacea and hence the bundle or bifurcation (Yater and Cornell, 1935; Warshawsky and Abramson, 1947). All these changes in some instances may be associated with complete atrioventricular block with or without left bundle branch block.

Rheumatic Heart Disease. The conduction system may be involved both in the acute and in the healed phase of the disease (Monckeberg, 1908; Mahaim, 1931, 1935; Campbell and Suzman, 1934; Gross and Fried, 1936; Crawford and Di Gregorio, 1947). In the acute phase, the general fibrositis, myocarditis and arteritis may involve the atrioventricular node and bundle, directly or by contiguity with the central fibrous body and the mitral and aortic annulus. It is alleged that such involvement of the tricuspid valve does not affect the conduction system (Mahaim, 1931). The above changes are usually correlated with mild to moderate disturbances in atrioventricular conduction, and rarely with complete heart block. In the healed phase, the conduction system may be involved by fibrotic phenomena originating from the aortic valve or the aortic leaflet of the mitral valve. Such changes usually involve the left or right bundle branches and less commonly and diffusely the node and atrioventricular bundle (Mahaim, 1935). Thus, partial or complete atrioventricular block is rare and left or right bundle branch block is more common.

Syphilitic Heart Disease. In syphilitic heart disease, the atrioventricular node, bundle and bundle branches may be involved in a gummatous or a nonspecific myocarditis (Krumbhaar, 1908-09; DeWitt, 1910; Nuzum, 1914; Mahaim, 1931; Rosenthal, 1932; Sohval, 1935; Braunstein *et al.*, 1940). In addition, there may be extension of lesions from the aortic valve or the sinuses of Valsalva. These lesions may be associated with excitatory electrocardiographic abnormalities such as active nodal rhythm, or with inhibitory phenomena

such as atrioventricular block (Mahaim, 1931). Likewise, in the healed or chronic phase of the disease, fibrosis of the atrioventricular node and bundle or bundle branches may lead to partial or complete atrioventricular block or bundle branch block.

Acute Inflammatory Disease of Heart. The conduction system may be involved by myocarditis of any origin and may be secondarily influenced by contiguity with endocarditis of the aortic and mitral valves. The conduction system may be involved along with the atrial and ventricular myocarditis (Monckeberg, 1908; Mahaim, 1931). Such involvement usually occurs in the more severe cases of general myocarditis (Figures IV-16-20). Opinions differ as to whether the conduction system can be exclusively involved in this disease (Marvin, 1925; Mahaim, 1931). The sinoatrial node is usually affected least, the atrioventricular node less than the atrioventricular bundle, and the bundle branches most (Rosenthal, 1932). However, in the conduction system the sinoatrial node may be involved exclusively, or the atrioventricular node maximally (Fleming and Kennedy, 1910-11). Thus, sinoatrial and atrioventricular conduction disturbances of an excitatory or inhibitory nature are common in myocarditis, producing sinoatrial, nodal or ventricular tachycardia, active nodal rhythm, partial

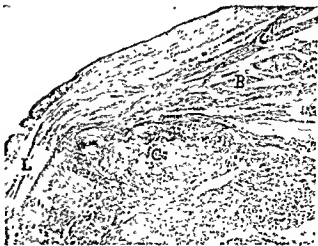


Figure IV-15. Section showing calcified mass pressing on termination of bundle and fasciculi of left bundle branch. Hematoxylin and eosin X50. B, Bundle, C, calcified mass in ventricular musculature, L, left bundle branch.

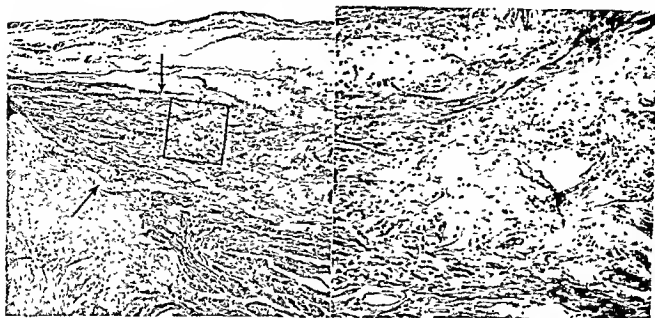


Figure IV-16. Section showing acute inflammation of AV node in myocarditis. Hematoxylin and eosin. *a* (left), X 30, *b* (right), X 150. Arrows point to the node. Area enclosed in square in *a* denotes region magnified in *b*.

or complete atrioventricular block, bundle branch block or sinoatrial block (Mahaim, 1931).

Myocarditis with involvement of the conduction system has been reported in diphtheria (Monckeberg, 1908, Fleming and Kennedy, 1910-11, Marvin, 1925; Stecher, 1929, Reid, 1930, Mahaim, 1931, Neubauer, 1943; Massey and Walker, 1948; Engle, 1949), scarlet fever (Monckeberg, 1908, Bernstein, 1938, Paul *et al.*, 1946), influenza (Dassen, 1933), pneumonia (Swift and Smith, 1937), typhoid fever (Dasseo, 1933, Logue and Hanson, 1945, Rantz *et al.*, 1946), typhus (Logue and Hanson, 1945), tuberculosis (DeWitt, 1910, Menon and Rao, 1945; Rantz *et al.*, 1946), mumps (Rosenberg, 1945), measles (Clark, 1948), German measles (Logue and Hanson, 1945), malaria (Rantz *et al.*, 1946, Kanatsoulis, 1948), and amebic hepatitis (Rawkins and Konstam, 1949). In diphtheria, the conduction system is often severely involved, with the production of partial or complete heart block. If the disease is not fatal, the conduction disturbance usually disappears. In a rare case, healing with permanent block has been described. In other types of myocarditis, milder forms of block are

more common than complete block, and the disturbances in conduction are evanescent.

In acute or subacute bacterial endocarditis, the inflammatory process may extend from the aortic or mitral valve to produce lesions in the atrioventricular node or bundle (Monckeberg, 1908, Mahaim, 1931, 1935; Rosenthal, 1932; Stenstrom, 1927), and may produce changes of an excitatory or inhibitory electrocardiographic nature (Mahaim, 1931). An added factor in the pathologic change may be the associated myocarditis. In pericarditis the sinoatrial node may be involved.

Neoplasms. The atrioventricular node, bundle and bundle branches may be compressed or replaced by primary neoplasms of the heart such as myxoma, angioma, sarcoma or metastatic tumor (Rosenthal, 1932; Mahaim, 1945, Leicher, 1948). Of rare occurrence is the primary tumor of the atrioventricular node, called lymphangioendothelioma by Monckeberg and celothelioma by Mahaim (1945). This neoplasm probably originates from the pericardial mesothelial lining, and is benign and self-limited. It usually replaces the greater part of the node and is associated with complete atrioventricular block.

Other Involvement of Conduction System. The sinoatrial and atrioventricular nodes, bundle and the beginning of the bundle branches may be involved by fatty infiltration (Monckeberg, 1908) of a greater degree than is normal for the age of the individual, or the atrioventricular node may lose its muscular connections with the atria, as a result of replacement by fat (Oppenheimer and Oppenheimer, 1914). In rare instances these changes may cause atrioventricular block (Spain and Cathcart, 1946). Likewise, fatty degeneration of the myocardium in anemia, diabetes mellitus or toxic states may involve the conduction system, especially the bundle branches (Monckeberg, 1908). Such involvement allegedly may be greater or less than that of the myocardium itself. In subendocardial hemorrhage, the right and left bundle branches are especially involved and their fibers separated but not destroyed. Likewise, in leukemia, infiltration may be found in the posterior part of the bundle and in the upper part of the left bundle branch (Monckeberg, 1908). In uremia, it is assumed that changes of unknown nature in the conduction system

account for the frequent incidence of atrioventricular block (Moore and Stewart, 1930; Kettner, 1947, Wright *et al.*, 1956). Likewise, it is thought that complete block in some cases of hemochromatosis (Petit, 1945) is related to pigmentary changes in the conduction system. Injury to the pericardium has rarely been associated with heart block (Coffen, 1930).

Correlation of Electrocardiographic Changes with Lesions in Conduction System. Several organized and many isolated attempts have been made in the last 50 years to correlate electrocardiographic findings with lesions in the conduction system. This has been done especially in atrioventricular block (Oppenheimer and Rothschild, 1917; Mahaim, 1931, Rosenthal, 1932; Cordero, 1934; Yater and Cornell, 1935; Yater *et al.*, 1936; Fiorio, 1939-40, Lev and Unger, 1953, Rossi, 1955), and right and left bundle branch block (Oppenheimer and Rothschild, 1917; Mahaim, 1931 and 1942; Rosenthal, 1932; Evans and Turnbull, 1937; Porto, 1938; Yater, 1938; Ad-darii *et al.*, 1945; Lenègre and Chevalier, 1949, 1951; Lenègre *et al.*, 1949, 1951; Lan-



Figure IV-17. Section showing acute inflammation of terminal portion of AV node and penetrating portion of AV bundle in myocarditis. Hematoxylin and eosin. *a* (left), X 30, *b* (right), X 150. Arrows point to bundle. Area enclosed in square in *a* denotes region magnified in *b*.



Figure IV-18 Section showing acute inflammation of AV bundle and beginning of left bundle branch in myocarditis. Hematoxylin and eosin. *a* (left), X 30, *b* (right), X 150.

Arrows point to the bundle. Area enclosed in square in *a* denotes region magnified in *b*.

geron *et al.*, 1950, Sanabria, 1950, 1953, Lenègre, 1952, Rossi, 1955), but also in paroxysmal tachycardia (Cowan *et al.*, 1913; Barnes and Yater, 1929, Yater, 1929b; Mahaim, 1931, 1932), atrial fibrillation and flutter (Schonberg, 1909, Hedinger, 1910, Draper, 1911; Cowan *et al.*, 1913; Yater, 1929) and nodal rhythm (Cohn, 1911-12; Cowan *et al.*, 1913).

Complete Atrioventricular Block. Permanent, complete atrioventricular block is almost always associated with an interruptive lesion either in the pre-atrioventricular nodal region, atrioventricular node, atrioventricular bundle, the bifurcation or both the left and right bundle branches. These lesions are usually related to hypertension and coronary disease, or sclerosis of the aortic valve or aortic leaflet of the mitral valve. In a group of paradoxical cases, allegedly complete destruction of the above structures did not lead to heart block (Mahaim, 1931). Likewise, cases have been reported of allegedly permanent complete

heart block without lesions or with partial lesions (Mahaim, 1931). Accordingly, nerve lesions (Rossi, 1955) or ischemia without histologic changes (Géraudel, 1925) have been postulated to explain the block.

Bundle Branch Block. Despite the excellent histologic studies of Mahaim (1931) and Yater (1938) on bundle branch block, correlation of necessity must largely begin with the era of precordial leads. Histologic studies before this era, however, reveal general unanimity that lesions of the bundle branches are usually bilateral.

Since the introduction of precordial leads, Sanabria (1950, 1953) and Langeron and his co-workers (1950) and especially Lenègre and his associates (1949, 1951, 1952, 1953) have studied bundle branch block. Sanabria found no correlation between the electrocardiographic pattern called bundle branch block and histologic lesions in the bundle branches. On the other hand, Langeron and

his colleagues found excellent correlation in one case. Likewise, Lenègre in a large series of cases found the following correlations: The electrocardiographic pattern called complete right bundle branch block is associated with major lesions in the right bundle branch, usually in the middle portion but occasionally at its beginning or at its terminal part. This type of block was found mainly in coronary, hypertensive and aortic disease, few cases having congenital, mitral or pulmonary disease. The electrocardiographic pattern called incomplete right bundle branch block, however, was rarely correlated with major alterations in the right bundle branch. This type of pattern was seen exclusively in congenital, mitral and pulmonary lesions. The electrocardiographic pattern was closely associated with right ventricular hypertrophy, although occasionally right ventricular hypertrophy was not present. These findings are in line with the hemodynamic studies of Braunwald and his associates (1956). Complete permanent

left bundle branch block was closely correlated by Lenègre with extensive lesions of the left bundle branch, although occasionally it was seen in patients with minimal or no lesions of the left bundle branch. This was found exclusively in association with aortic, coronary or hypertensive lesions. Not a single case of heart disease favoring the hypertrophy of the right ventricle was found in this group. The left bundle branch was generally involved at its origin, but sometimes more distally. Likewise, incomplete left bundle branch block was usually correlated with severe lesions of the left bundle branch, although a few cases showed mild lesions, and in an occasional case no lesion was found. This was again the case in aortic, coronary and hypertensive disease. The contralateral branch in all these abnormalities was normal or minimally involved. On the contrary, Mahaim (1931) and Yater (1938) believe that unilateral lesions are rare. In bilateral or unstable bundle branch block, Mahaim (1942)



Figure IV-19. Section showing acute inflammation with marked necrosis of fibers of left bundle branch in myocarditis. Hematoxylin and eosin. X300. Arrows point to some necrotic fibers.



Figure IV-20. Section showing acute inflammation of right bundle branch in myocarditis. Hematoxylin and eosin. *a* (left), X 30, *b* (right), X 150. Arrows point to right bundle branch in *a*, which is the area depicted in *b*.

and Lenègre (1952) have found lesions in both bundle branches.

In agreement with Sanabria (1953), Glomset and associates (1944), Glomset and Birge (1948) and Rossi (1955) do not feel that the electrocardiographic pattern of bundle branch block has an anatomic basis in the conduction system. Rossi (1955) has postulated that the basic lesion may lie in pathologic changes in the nerves of the conducting system.

Other Arrhythmias. In paroxysmal tachycardia, atrial fibrillation and atrial flutter, acute inflammatory changes have been described in the sinoatrial or the atrioventricular node or in both nodes. However, in the opinion of Yater (1929b) and Monckeberg (1924), there is no known common anatomic basis for these electrocardiographic abnormalities. In nodal rhythm, lesions have been described in both the sinoatrial and atrioventricular nodes.

Effects of Conduction Disturbances upon

Function of Heart. Complete heart block *per se* produces slight to moderate hypertrophy of the heart (Campbell and Suzman, 1934). This is related to an increase in stroke volume with a normal minute volume (Alt *et al.*, 1930, Smith *et al.*, 1930). Thus, there is a slight elevation of systolic and a fall in diastolic pressure (Butler and Levine, 1930).

Since acquired heart block is usually associated with organic disease of the ventricular myocardium, the prognosis is related to the degree of integrity of the myocardium, and its ability to initiate an independent rhythm. Where such disease is relatively lacking, as in congenital heart block, the block permits long survival. Bundle branch block *per se* is not known to alter appreciably the function of the heart. Severe tachycardias of any kind which markedly increase the ventricular rate may seriously affect the cardiac output, but may not in themselves be associated with any remarkable morphologic change in the heart.

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Physiology of the Heart

A. Normal Cardiac Physiology

HAROLD D. GREEN

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1. INITIATION AND CONDUCTION OF CARDIAC IMPULSE

Specialized Tissue

FOR GROSS and microscopic description of the Conduction System, see Chapter IV.

Electrical and Mechanical Units. If a portion of myocardium from either atrium or ventricle is attached between two hooks, one fixed and one attached to some form of transducer, it is possible to record the contractile effort of the tissue when it is excited. If a suitable amplifier and recording galvanometer are connected (a) to a micro-electrode which has been inserted through the cell membrane

and (b) to another electrode which makes contact with the exterior of the cell, it is possible to record the simultaneous changes in transmembranal potential which occur during excitation and response. Figure V-1 is a schematic diagram of the contraction and of the transmembranal potentials recorded in atrial tissue by this method of Hollander and Webb (1955). In these experiments, the resting potential, representing the difference in potential recorded during diastole compared to that recorded by the same pair of electrodes when both were in contact with the exterior of the

cell, had an average value of 62 millivolts, with the interior negative with respect to the exterior. During activity of the atrial tissue, the interior became negative with respect to the exterior, the average overshoot was 13.2 millivolts, and the action-potential lasted, on the average, 61.7 milliseconds.

Site of Primary "Pacemaker." Anatomic studies (see Chapter IV) have demonstrated specialized tissue in the right atrium at its junction with the superior vena cava, which is designated the *sinoatrial node*. Numerous physiologic studies have shown that this tissue is the site of the normal pacemaker of the heart.

Secondary "Pacemakers." If the excitability of the sinoatrial node is relatively depressed, one of the several regions that ordinarily have lower excitability may serve as the pacemaker. In order of descending excitability, these regions are the atrioventricular (A-V) node, the A-V bundle above the bifurcation of the conduction system, the atrial tissue, the branches of the A-V bundle, and the ventricular musculature. The cardiac rate, with the sinoatrial node as pacemaker, may vary from 45 to 170. The inherent cardiac rate with initiation of impulse in the atrioventricular node or the common bundle, i.e., nodal or supra-ventricular rhythm, is 30 to 60 (usually 35 to 50) per minute. When the pacemaker is located in the ventricle (presumably in one of the bundle-branches), the inherent rate is usually of the order of 20 to 30 per minute. (See also Table V-1, page 207.)

Mechanism of Action of Pacemaker. Transmembranal action-potentials have been recorded from micro-electrodes inserted into the tissues that serve as pacemakers (Figure V-2A). The difference in potential may amount to 100 millivolts at the moment of maximum repolarization (diastole) when the interior of the tissue is negative with respect to its exterior. The difference in potential then slowly decreases to a critical level at which depolarization abruptly occurs (systole) and the recording line crosses the line of zero potential. Repolarization begins after a brief pause. Non-pacemaking tissue (Figure V-2B) shows a similar cyclic change in potential, except

that a period of constant potential persists after repolarization is completed, i.e., the curve is flat. Apparently the rate at which a pacemaker "fires" is determined by (a) the slope of the differences in potential during diastole (the more rapid the decrease in transmembranal potential, the earlier the initiation of the next impulse), and (b) the degree of instability of the tissue (Brooks *et al.*, 1955).

Conduction of Cardiac Impulse

Conduction in Atrium. The mammalian atrium has no special conduction path. The cardiac impulse spreads centripetally at the rate of 60 to 120 cm. per second, allowing the wave of electrical negativity to reach the right auricle (atrial appendage) approximately 0.03 second, the left auricle 0.045-0.06 second and the A-V node 0.02-0.045 second, after the initiation of the impulse in the S-A node.

Conduction in Atrioventricular Node. Precise measurements of the rate of conduction through the A-V node are not available because of the inaccessibility of the node (Scher, 1955). It may be assumed that the impulse is conducted slowly, requiring at least 0.05 second. The cardiac impulse passes readily

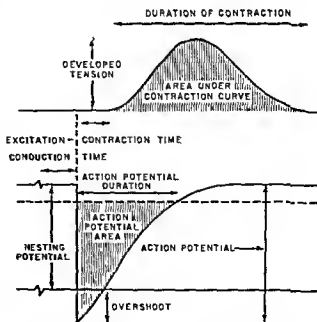


Figure V-1. Diagram of a typical record showing the relation between action potential and contraction. For description, see text. (Reproduced from Hollander and Webb, 1955)

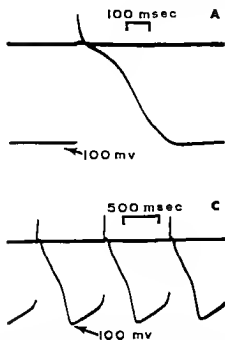


Figure V-2 Transmembranal action-potentials of single Purkinje fibers. A indicates induced activity in a quiescent preparation; C, spontaneous activity recorded from a pacemaker area. (Reproduced from Brooks *et al.*, 1955)

from atrium toward ventricle; but normally it passes in the reverse direction with difficulty, if at all. Occasionally an accessory path with a faster velocity of conduction allows pre-excitation of a portion of the ventricle, giving rise to the Wolff-Parkinson-White syndrome of short P-R interval and prolonged QRS (reviewed by Soulie, 1954).

Conduction in Ventricles. The impulse in the subendocardial muscle and at least one-half of the thickness of the adjacent free ventricular wall spreads at the rate of 1.5 to 5.0 (average 1.8) meters per second. The average rate of conduction at right angles to the wall is 300 mm. per second. There is no preferential spread along muscle bundles, compared to that at right angles to the superficial fibers.

The earliest activity occurs on the left side of the interventricular septum (Figure V-3). Much of the septum is excited by double envelopment from both endocardial surfaces, correlating with the Q wave in lead II of the electrocardiogram (Scher *et al.*, 1955). The points of earliest activity in the wall are on the endocardial surfaces of both ventricles at the junction of the free wall and septum in the mid-anterior region. The excitation spreads through both base and apex to-

wards the left and right sides and from within, outwards (Scher *et al.*, 1953, 1955; Sodi-Pallares *et al.*, 1955). The last area to be activated is the basal portion of the septum (Scher and Young, 1956). Fibrosis or other change may constitute a barrier to the normal spread of conduction (Scher *et al.*, 1955).

Mechanism of Conduction. Conduction of the impulse in the heart, like that of nerve, is propagated in waves. The rate of propagation is dependent on the properties inherent in each portion of the tissue through which the impulse travels. Following excitation, a period elapses during which the membrane will not respond to an impulse or other form of stimulus. This interval is designated the *absolute refractory period*. A relative refractory period then follows during which the membrane will respond only to a stimulus that is stronger than normal (Hoffman *et al.*, 1957).

The recovery of membrane-potential during the refractory periods is not a wave-like phenomenon or conducted impulse but is dependent upon the local metabolic activity at each point. Changes in the rate of recovery, and inversely, therefore, of the duration of the refractory period, frequently parallel changes in the velocity of propagation of the impulse, but the two are probably not causally related. Impulses which are initiated during the relative refractory period are conducted at a rate which is slower than normal. When the absolute refractory period of a portion of the conduction system becomes longer than the interval between two cardiac impulses, the second of the two impulses dies out as it reaches an area which is still refractory, producing a form of heart block (see page 204).

Ventricular Excitability

Law of "All or None." If a quiescent ventricle is subjected to a series of single stimuli which are progressively increased in strength and spaced not closer than one per second, no contraction will result until a certain intensity is reached—the threshold stimulus. Further increase in intensity of stimulus will not, however, increase the strength of the response. The ventricle, therefore, responds maximally or not at all to a given stimulus. In this regard and despite its multinucleated, multifibrillated structure, it behaves like a single skeletal muscle fiber, rather than a skeletal muscle composed of many fibers.

Refractory Period of Ventricle. Like the conduction tissue noted above, the ventricular myocardium becomes completely refractory upon responding to a stimulus and remains refractory until or shortly after, the beginning of relaxation. A relative refractory period then follows in which excitability gradually returns to normal (Brooks *et al.*, 1955, van Dam *et al.*, 1956). It is thus impossible to induce a state of complete tetanus in cardiac muscle even with rapid, strong stimuli. However, with rapid repetition, some of the stimuli will fall in the "vulnerable" period of a previous contraction, *i.e.*, early in diastole, and may start a continuously moving impulse which keeps traveling about the ventricle im-

mediately after the preceding response and thus establishes the state known as *ventricular fibrillation* (see page 202). The refractory period shortens with increase in heart rate and lengthens with slowing and with strengthening of the heart beat. The changes are principally in the absolute refractory period, with little change in the relative refractory period (Brooks *et al.*, 1955). The refractory period tends to be shortest in atrial tissue, intermediate in the ventricular muscle and longest in the nodal tissue. Variations in refractory period, particularly of nodal tissue, play a part in the genesis of certain arrhythmias (see Part B, Abnormal Cardiac Function).

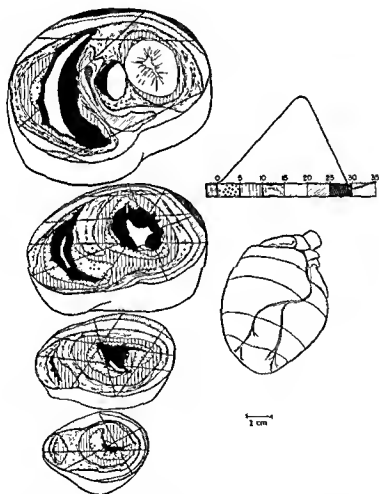


Figure V-3. Diagrams illustrating the spread of excitation in the two ventricles, as shown by insertion of multiple contact needles in various directions through the walls of the heart as indicated by the solid lines. The time scale corresponding to the shading is indicated in the diagram in the upper right, and the position of sections in the diagram in the lower right. The figures in the time scale represent milliseconds. (Reproduced from Scher and Young, 1958.)

2. CARDIAC CYCLE

Pressure and Volume Curves

An understanding of the events in the cardiac cycle may be derived from study of simultaneous records of cardiac volumes and pressures within the pulmonary trunk, atria, atria and ventricles (Figure V-1).

Methods for Cannulating Cardiac Chambers. Pressure curves in animals were first obtained by inserting cannulae into the cardiac chambers through their walls. A similar technique has been used in persons undergoing surgery for pulmonary disease (Braunwald *et al.*, 1956). More commonly pressures are recorded from the right atrium and ventricle and pulmonary trunk in man by passing catheters into these chambers by way of the antecubital vein and the superior vena cava under fluoroscopic guidance (Cournand *et al.*, 1944; Richards, 1946; Dexter, 1947; and Sosman, 1947). Pressures have also been recorded from the left ventricle of man by a catheter passed toward the heart by way of a carotid artery and then retrograde through the aortic valve (Zimmerman *et al.*, 1950) and by direct transthoracic ventricular puncture (Buchbinder and Katz, 1949).

Pressures in the left atrium of man have been recorded by means of a needle inserted into the atrium by way of the trachea (Gunning and Linden, 1958). This technique has also been employed to insert needles into the aorta and pulmonary trunk (Allison and Linden, 1955). Fine catheters have been passed into the left ventricle by means of needles inserted through the wall of the pulmonary vein or left atrium (Björk and Malmström, 1954; Connolly *et al.*, 1954). This technique is useful in the study of patients with mitral and aortic valve disease. However, the puncture may cause major complications, such as cardiac tamponade, ventricular fibrillation, cerebral embolism, pneumonia and pericarditis, and should, therefore, be used only when the information to be obtained is necessary for a decision as to surgical exploration (Bagger *et al.*, 1957).

"Pulmonary capillary pressure" ("P.C.P.—wedge pressure") is recorded by passing a catheter by way of the right atrium, right ventricle, and pulmonary trunk until it becomes lodged in a small branch of one of the pulmonary arteries (Hellems *et al.*, 1948; Gorlin and Haynes, 1950). "Wedge pressure" is believed to be a reasonably accurate reflection of the magnitude and contour of the left atrial pressure in man in both normal and assisted respiration (Connolly *et al.*, 1954; Wilson *et al.*, 1955). "Wedge pressures" have been recorded by catheters passed in a similar manner in the reverse direction into a pulmonary vein. Such pressures are usually lower than the mean pressure in the pulmonary trunk and exceed the mean left atrial pressure. A positive correlation exists between the pulmonary arteriolar resistances and the difference between the wedge pressures in the pulmonary veins and those in the pulmonary trunk. The oxygen saturation of blood from the pulmonary-vein wedge catheter uniformly exceeds that of the left atrial blood and usually that of the blood of the pulmonary vein (Connolly and Wood, 1955; Wilson *et al.*, 1955; reviewed by Gregg, 1955).

Right atrial pressure can be estimated by a manometer connected to a needle inserted into an antecubital vein only when the subject is supine and all portions of the vein between the needle and the heart are below the level of the heart. With the subject sitting, the internal pressure in the vein as it passes over the upper portion of the thoracic cage is less than atmospheric pressure and the vein therefore collapses. The needle is thus no longer connected by a continuous column of fluid with the heart and cannot correctly record atrial pressure (Davis and Shock, 1949).

Pressure Manometers. Various forms of pressure manometers have been attached to such cannulae and catheters for making a permanent record of the pressures at each instant in the heart cycles. The types most commonly used at the present time are all membrane-manometers. In the case of the optical manometers, flexing of the membrane causes a light beam, reflected from a mirror attached to the membrane, to move trans-

versely across a strip of photographic paper which is moving vertically. In the direct-writing type of pressure-manometer, the membrane is attached to a resistance or capacitance unit in such manner that the resistance or capacitance varies with the degree of flexing of the membrane. The fluctuations in resistance or capacitance are amplified and then fed into some form of recorder, such as a cathode ray oscillograph, an ink-writing oscillograph, or one that writes by passing a heated stylus over plastic-coated paper (Green, 1950a; Lambert, 1950). A minute manometer which can be inserted directly into the cardiac chambers has been devised by Ellis and associates, (1951). It is attached to the tip of a cardiac catheter, has the same caliber as the latter, and gives faithful reproduction of intravascular pressures.

Standard Zero Reference Plane for Measuring Pressure. The numerical value obtained from measurements of pressure in the cardiovascular system depends, of course, upon the horizontal plane to which zero pressure is referred. Most commonly this has reference to the assumed level of the center of the atrium. Stead and associates (1945) place this plane 5 cm. posterior to the fourth costochondral junction, with the subject supine. McMichael and Sharpey-Schafer (1944) used the posterior surface of the thorax. Holt (1940) determined the level of the meniscus of a saline manometer, with the subject prone, then supine, and placed the reference plane half-way between the levels assumed by the menisci in the two positions. A reference plane 10 cm. ventral to the skin of the back with the subject supine (Green, 1950b) appears to be the one most generally used and I shall, therefore, refer to it as the *standard zero reference plane*.

Measurement of Internal Diameters of Ventricle. The internal diameter of the ventricles has been measured throughout the heart cycle in anesthetized and unanesthetized dogs by gauges attached between opposing walls of the ventricular cavities in various directions using electrically recording strain gauges (Rushmer, 1954, 1956a).

Ventricular and Atrial Pressures. Ventricu-

lar Volume. The events portrayed in Figure V-4 are applicable to both the left and right chambers of the heart, except that the magnitude of the pressures are less in the right chambers.

The rate of entrance of blood into the ventricles, particularly during rapid inflow, is a function of the pressure in the atrium and of the rate of relaxation of the ventricle, i.e., of the acceptance of the ventricle. Some investi-

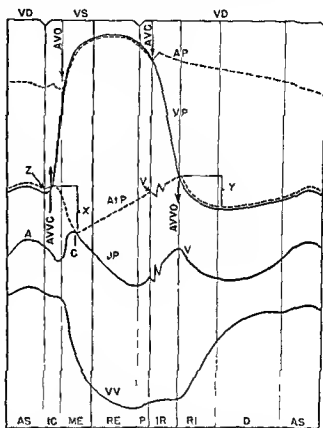


Figure V-4. Relationship between aortic pressure AP, intraventricular pressure VP, atrial pressure AIP, jugular ven pulsations JP, and changes in ventricular volume VV, during a heart cycle. VD, ventricular diastole, VS, ventricular systole, AS, atrial systole; IC, isometric contraction; ME, maximum ejection; RE, reduced ejection; P, protodiastole, IR, isometric relaxation; RI, rapid inflow; D, diastasis. AVVC, atrioventricular valve closes, AVO, aortic valve opens; AVC, aortic valve closes; AVVO, atrioventricular valve opens. A, atrial (presystolic) wave; C, carotid (systolic) wave; V, ventricular (diastolic) wave, Z, point in atrial pressure corresponding to beginning of ventricular contraction, X, drop in atrial pressure during atrial relaxation; Y, drop in atrial pressure during rapid emptying of atrium into ventricle. These curves are schematic and have been exaggerated, particularly the atrial pressure curve, in order to accentuate the various deflections. (Reproduced from *Medical Physics*, Green, 1950, modified after Little *et al.*, 1948, and Opdyke *et al.*, 1948.)

gators claim that the relaxation of the ventricle can actually suck blood into the ventricle but I doubt if true suction, *i.e.*, an intra-ventricular pressure less than extra-ventricular pressure, ever truly occurs outside of unusual laboratory conditions.

The pressure in the left ventricle oscillates between 5 mm. of mercury diastolic and 90 to 140 mm. of mercury systolic in the course of the normal heart cycle. The pressure in the right ventricle in man normally varies between 19 and 27 mm. of mercury systolic and -0.5 and $+6$ mm. of mercury diastolic with reference to atmospheric pressure at the standard zero reference plane (see above) (Battro *et al.*, 1949; Richards, 1949, Dexter *et al.*, 1950). The pressure in the atrium and ventricle just at the moment of onset of ventricular systole, *i.e.*, just before closure of the atrioventricular valve, is called the "end diastolic pressure." In both man and animals this pressure is usually higher in the left chambers than in the right chambers. The pressures in the right atrium oscillate with respiration between -7 and $+16$ mm. of mercury measured with reference to atmospheric pressure at the level of the standard zero reference plane, with the person supine. (See page 171.)

Pulmonary Capillary Pressure ("Wedge Pressure"). (See page 170.) The left atrial pressure has been thought to be closely approximated by measurement of "pulmonary capillary pressure." However, recent studies suggest that when left atrial pressure is unusually high, as in the presence of mitral stenosis, the pulmonary capillary pressure may be only approximately half the true atrial pressure (Murphy, 1958). The normal value for "pulmonary capillary pressure" is 5 to 12 mm. of mercury, the average value being 6 to 9 mm. (Hellems *et al.*, 1948; Dexter *et al.*, 1950). By simultaneous measurement of pulmonary capillary pressure and cardiac output, Gorlin and Haynes (1950) believe they can estimate accurately the cross-sectional area of the mitral valve. For these estimates they assume left atrial pressure to be 5 mm. of mercury with reference to the standard zero reference plane, with the subject supine.

In both man and dog, direct atrial puncture usually yielded pressures in the left atrium which exceeded those of the right atrium throughout most of the atrial cycle. This difference was usually greatest at the "V point" (Opdyke *et al.*, 1948; Braunwald, *et al.*, 1956). Opdyke and associates explain the higher pressures on the left side as a result of the left veno-atrial system being less distensible than the right. My own interpretation is that a slightly higher end-diastolic pressure is required by the left ventricle than by the right ventricle to maintain equal stroke-volume outputs.

Time Relations in Man. Records of the events in the human heart, obtained by direct puncture of the four chambers during operation for pulmonary disease (Figure V-5) indicate that contraction of the left atrium begins before contraction of the right atrium, while contraction of the left ventricle begins after, but is completed before, that of the right ventricle (Braunwald *et al.*, 1956).

Jugular Venous Pressure. Jugular venous pressure (Figure V-4, JP) is practically identical with atrial pressure except for the presence of a sharp rise in pressure that corresponds with the onset of ventricular ejection, which is produced by the impact of the underlying carotid artery as it expands with the rising aortic pressure. The A (P) wave is absent in atrial fibrillation; since the triple wave may be seen readily with a normal heart, the presence of a double, instead of a triple, wave makes it possible to diagnose atrial fibrillation clinically. The amplitude of the A wave is increased during augmented venous return and decreased during diminished venous return.

Pressure in Aorta and Pulmonary Trunk. As the result of the ejection of blood into the aorta in an intermittent stream, the pressure in the central aorta pulsates with each heart cycle (Figure V-4). The notch corresponding to the closure of the aortic valve is called the incisura, the bottom of the notch marking the moment when the aortic valve closes. A slower wave of rising and falling pressure, frequently recorded following the incisura, is caused by the reflection from distant bifurcations of the wave generated by the preceding ventricular ejection. With slow heart rates, a second slower

wave may be noted just before the next systole. This wave may be a reflection of the dirotic wave from the periphery. Waves of still higher frequency may be superimposed on the systolic phase of the aortic pressure curve, produced by reflections of the peripherally propagated initial pressure rise from nearby arterial bifurcations. The pressure in the pulmonary trunk undergoes similar oscillations.

Method for Obtaining Systemic Arterial Pressure. The precise pressure in the systemic arteries is best obtained by inserting a needle into an artery and connecting the needle with a suitable recording manometer. For practical purposes the arterial pressure may be estimated with the clinical sphygmomanometer. At a pressure just below systolic pressure, a short pulse of blood flows under the cuff of the sphygmomanometer and gives rise to a sound (the first phase) which can be heard with a stethoscope placed over the artery just distal to the cuff. As the cuff pres-

sure is lowered, the sound becomes louder, thumping and roaring (second and third phases). At still lower cuff pressures, the sound suddenly diminishes in intensity (fourth phase), then at a pressure about 5 to 10 mm. of mercury lower, disappears entirely (fifth phase). Opinions differ as to whether the fourth or fifth phase should be taken as signaling the correct diastolic pressure, but the majority favor the fifth phase. It is probably better to record both. To obtain reasonably satisfactory readings the person should be seated, the cuff should be at least 12 cm. wide for use on the adult arm (a wider cuff would be preferable for persons with large fatty arms), and the arms should be relaxed and slightly abducted.

Normal Values of Arterial Pressure. According to Dublin and associates (1950), among persons in their twenties, systolic pressure ranges normally from 95 to 120 mm. and diastolic pressure, from 62 to 88. These values increase progressively with age, the increase

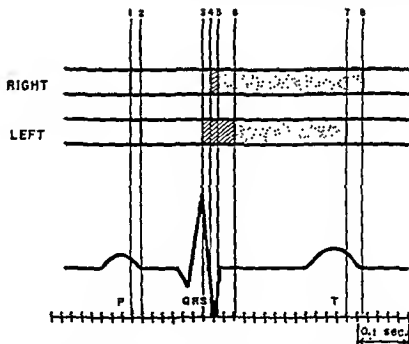


Figure V-5. Diagrammatic representation of electrical and mechanical events in the right and left atria and ventricles in normal persons. 1, onset of right atrial contraction; 2, onset of left atrial contraction; 3, onset of left ventricular contraction; 4, onset of right ventricular contraction; 5, onset of right ventricular ejection; 6, onset of left ventricular ejection; 7, end of left ventricular ejection; 8, end of right ventricular ejection. The striped areas represent ventricular isometric contraction, the stippled areas, ventricular ejection. (Reproduced from Braunwald, Fishman and Courmand, 1956)

in systolic pressure becoming more rapid about age 50, so that in the age group 60 to 64, normal systolic pressure ranges between 115 and 170 and diastolic pressure, between 70 and 100. In a given individual, the pulse pressure (systolic pressure less diastolic pressure) closely parallels stroke-volume output of the heart. The pressure in the pulmonary trunk varies normally between 19 and 27 mm. of mercury, (average, 23 mm.) systolic, and 6 to 12 mm. of mercury (average, 9 mm.) diastolic (Hellems *et al.*, 1948, Dexter *et al.*, 1950).

Peripheral Arterial Pressure. The aortic pulse is transmitted through the aorta and large arteries at a velocity of 5 to 10 meters per second. As the pulse wave approaches the large peripheral arteries, such as the radial or femoral, the peak of the wave occurs progressively earlier, relative to the start of the rise of pressure. The peak is also higher and sharper than that in the arch of the aorta. This wave is reflected back from these peripheral arteries to the arch of the aorta, forming the slow wave noted there following the incisura. It is then reflected back to the peripheral vessels forming the dicrotic wave (Figure V-6) (Hamilton, 1950).

The dicrotic wave, in turn reflected back toward the aortic arch, may be responsible for the late diastolic wave in the central aortic pressure curve. The forward and backward undulations, superimposed on the main cardiac pulse beat in the aorta, are called the standing waves (Hamilton, 1944) or the resonant waves (Spencer *et al.*, 1958).

Cardiac Movements

The apical portion of the pericardium is rigidly attached to the relatively fixed diaphragm, whereas the basilar portion of the pericardium is attached to the superior mediastinal blood vessels and other structures which are distensible. Thus, since no space may be present between the epicardium and pericardium, the apex remains in contact with the diaphragm, whereas the base descends with each ventricular systole.

The myocardial fibers are arranged spirally.

As a consequence, the heart rotates on its vertical axis with each systole, producing the apical thrust noted on palpation of the chest. The apical thrust is also thought to be due to recoil of the apex of the heart as the blood is ejected from the ventricles. The thrust can be divided into two components. The first begins about 0.08 seconds after the beginning of electrical excitation, owing to the recoil of the right ventricle. The second begins about 0.11 seconds after the onset of electrical excitation, and about 0.01 second before the beginning of the carotid artery upstroke; it is believed to be of left ventricular origin (Edleman *et al.*, 1957).

Roentgenkymography and Electrokymography. The movements of the borders of the cardiac chambers and great vessels and the pulsations of the lung fields have been recorded by roentgenkymography and electrokymography. In the former, an x-ray cassette is moved vertically past a series of narrow, horizontal slits about a centimeter apart in a lead shield during a continuous x-ray exposure. The resulting x-ray film shows a scalloped silhouette for the heart, from which one can interpret changes in lateral movement of the cardiac silhouette.

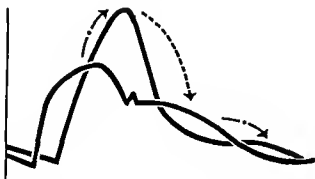


Figure V-6. Pressure curves recorded simultaneously from the aortic arch (curve which rises first) and from the femoral artery. The first arrow (—•→) indicates the pressure "peak" which is transmitted from the aortic arch to the region of the femoral artery. The second arrow (---•→) indicates the reflection of the pressure "peak" in the femoral artery region back to the aortic arch, producing a post-incisural rise of pressure in the latter region. The third arrow (—•→) indicates the reflection of the post-incisural "peak" in the aortic arch region back to the femoral artery region to produce the dicrotic wave. (Redrawn after Hamilton, 1944, 1950.)

In the electrokymograph, a photomultiplier tube records the light emitted from a narrow strip of fluorescent x-ray screen placed at right angles to a border of the heart and radiated by an x-ray beam directed through the chest. The resulting record reproduces the movement of the border and has proved useful in the interpretation of normal and abnormal cardiac and vascular movements (Boone *et al.*, 1949; Gillick and Schneider, 1949).

Cardiac ventriculography. X-ray visualization of the cardiac chambers is made possible by the intravenous injection of a radiopaque substance during fluoroscopy or while making x-ray films. However, direct injection into one or the other ventricle by transthoracic puncture may provide more precise information regarding the presence and magnitude of mitral or tricuspid regurgitation, or of a left ventricular aneurysm (Lehman *et al.*, 1957).

Heart Sounds

First Heart Sound. The first heart sound is produced primarily by the snapping shut of the two atrioventricular valves at the beginning of isometric contraction (Dock, 1945). Contributory factors may be the sudden development of tension in the ventricular muscle and the chordae tendineae (Orias, 1949). Rushmer (1957) suggests that contraction of the papillary muscles contributes to the first sound by pulling the atrioventricular leaves together. The sound caused by closure of the mitral valve is heard best at the point of apical impact, usually in the fifth interspace in the midclavicular line. The sound from the closure of the tricuspid valve is heard best in the sixth interspace just to the right of the sternum. The interval from the beginning of rise of ventricular pressure to the beginning of the first heart sound is minimal with a normal period between atrial systole and ventricular systole. In ectopic beats of the ventricle or in absence of the atrial beat, the interval is significantly increased. It is thought that with normal ventricular beats, the orifices of the atrioventricular valves are nearly closed prior to ventricular systole by

the preceding atrial systole, whereas in the absence of an immediately preceding atrial beat, the open orifices of these valves must be closed by ventricular systole (Little *et al.*, 1954; Gregg, 1955).

Second Heart Sound. The second heart sound, produced by closure of the aortic valve, is heard best in the second right interspace; that produced by closure of the pulmonary valve, in the second left interspace. A split second sound may be produced when the two semilunar valves close asynchronously (Orias, 1949).

Third Heart Sound. The third heart sound is associated with the rapid inrush of blood into the ventricle during the descending limb of the V wave of the jugular and atrial pressure curves. The third heart sound is also believed to result from vibration of the ventricular walls because of their sudden distension (Boyer, 1942; Orias, 1949), from sudden tensing of the atrioventricular valves by a wave reflected from the ventricular walls (Dock *et al.*, 1955), and from tensing of the pericardium (Dunn and Dickerson, 1955).

It is recordable in from 26 to 85 per cent of normal persons, depending on the sensitivity of the recorder to vibrations of low frequency. A third heart sound, designated as an "opening snap" may be present 0.04 to 0.12 second after the onset of the second sound. It is most common in the presence of mitral stenosis and may even be the only auscultatory sign of mitral stenosis (Warren *et al.*, 1958). In some instances, gallop rhythm results from intensification of the third heart sound (see below).

Fourth Heart Sound. The fourth heart sound is associated with contraction of the atrium. It has been recorded in 27 per cent of normal persons. It is audible in persons having left ventricular hypertrophy associated with hypertension. It may be produced by rapid flow of blood through the atrioventricular valve or by the sudden distension of the ventricle or by a rebound closure of the atrioventricular valve following the rapid inflow accompanying atrial systole (Scherlis, 1946; Weitzman, 1955).

Intensity of Heart Sounds. The intensity of

the first heart sound (a) is augmented with increased cardiac output or elevated aortic pressure and is diminished in myocardial damage from any cause; (b) is related to the interval between the atrial and ventricular systoles (in general, the longer the interval, the louder the first sound, Levine and Harvey, 1949); (c) is louder after a short diastole than after a long diastole, i.e., if it occurs during the phase of rapid ventricular filling (Rytand, 1949, Fishman and Courmand, 1953); (d) is frequently intensified with tachycardia, emotional tension, hyperthyroidism, anemia, infections and fever (Levine and Harvey, 1949); (e) is loud and snapping in the presence of mitral stenosis, and (f) is louder the more the atrioventricular valve leaflets are separated at the onset of ventricular systole, i.e., when the interval between atrial and ventricular systole is longer than normal (Siecke and Essex, 1958).

The intensity of the second sound is related to the pressure in the appropriate vessel at the onset of isometric relaxation. Normally, the aortic second sound in adults is louder than the pulmonic, but in left heart failure or mitral stenosis, the reverse may be found. In dilatation of the root of the aorta resulting from advancing age, the aortic second sound frequently has a tympanitic tone. The second aortic sound is decreased in aortic stenosis (Levine and Harvey, 1949). The first and second sounds may be split or even duplicated, probably because of asynchronous onset or cessation of contraction in the two ventricles. This may be seen particularly in bundle branch block or ventricular premature beats. The intensity of both the first and second sounds is louder in thin-chested persons and softer in those with thick chests.

The intensity of the various component frequencies in the heart sounds has been analyzed by Foulger and associates (1947). They recorded a fairly large component of sounds of low frequency and found that, in general, increased cardiac work tended to augment the intensity of sounds of higher frequency. Various attempts have been made to calibrate the intensity of cardiac sound (Sloan and

Greer, 1955; McGregor *et al.*, 1956), including recording the envelope of the sound, (sonovelocity, Rushmer *et al.*, 1954), but as yet there is no general agreement upon a standard (Luisada and Gamna, 1954; Schaefer, 1956). However, the registration of heart sounds (phonocardiography) has proved useful in training the physician to hear and interpret sounds which would otherwise be overlooked, and in providing a permanent record which can be studied later and used as an aid in education (McKusick, 1957).

Gallop Rhythm. Occasionally, a third heart sound is heard which gives rise to a triple beat that resembles the hoof beats of a galloping horse. The third sound may be produced in early diastole during the phase of rapid inflow into the ventricle which follows opening of the atrioventricular valves (early ventricular or protodiastolic gallop). Ventricular gallop is most frequently associated with incipient or actual congestive failure; it may be caused by a momentary rise of ventricular pressure above atrial pressure, with temporary closure of the atrioventricular valve. Ventricular gallop may be made to disappear by reducing cardiac output by standing, or by occlusion by tourniquet of the veins in the extremities. A presystolic or atrial gallop is produced by a third heart sound which occurs during atrial systole. This sound is heard frequently in patients with hypertension, myocardial infarction or heart block. If the heart rate is rapid enough, the protodiastolic and presystolic phases may practically coincide, giving a summated effect which may be more readily audible as a third heart sound and producing a mid-diastolic gallop rhythm (Braun-Menendez, 1938, Levine and Harvey, 1949, Warren *et al.*, 1958). Systolic gallop rhythm is less common than diastolic gallop rhythm. It is generally loudest at the apex, usually with the patient recumbent. The exact cause of systolic gallop is not known; it is not believed to indicate a grave prognosis (Levine and Harvey, 1949). When heard loudest at the aortic area, it may be the result of impact of the aorta against other structures (Wolferth and Margolies, 1940).

3. CARDIAC OUTPUT

Cardiac output may be defined as the volume of blood (in ml. or l.) ejected by a ventricle per minute. Under normal circumstances the output of the two ventricles per minute is the same and is, of course, equal to the volume of blood circulated through the body per minute. However, in aortic insufficiency, septal defects and patent ductus arteriosus, the outputs of the two ventricles differ from each other and from the volume circulated per minute. The cardiac output is, of course, the product of the heart rate times the average stroke volume (output per beat). Cardiac output is a function of the size of the individual. To allow for this, the output is usually expressed as the cardiac index, which is the output in liters per minute per square meter of body surface. While the output of the two ventricles is the same over a period of time, *i.e.*, one or more minutes, the output of the ventricles differs from beat to beat, owing to the difference in the effects of inspiration and expiration on the filling and emptying of the two chambers.

Methods for Measuring Cardiac Output in Man

Foreign-Gas Techniques. Indirect Fick Principle. The earlier measurements of cardiac output in man were made with the foreign-gas techniques (Green, 1948a).

$$CO \text{ (in ml/min)} = \frac{63 \times \text{ml (gas absorbed)} / (\text{seconds for rebreathing})}{\text{ml gas/ml of arterial blood}}$$

Since the rebreathing could alter the cardiac output, the foreign-gas technique was subsequently modified in order to use it to determine the average concentration of oxygen in the venous blood, and the output was then calculated as for the direct Fick principle (see below; Grollman, 1932). Both the above techniques assume that the venous blood at no time contains any of the foreign gas. Unfortunately, recirculation always occurs, causing the actual arteriovenous difference in concentration of foreign gas to be smaller by about 24 per cent than is indicated by analysis of the arterial sample alone. The rebreathing also abnormally elevates the arterial concentration of oxygen. As a result, the cardiac output measured

by this technique is always too low by about 33 per cent (Hamilton, 1945; Chapman *et al.*, 1950).

Direct Fick Principle. In the direct Fick principle, a sample of arterial blood is obtained by a needle inserted in the radial artery, and a sample of mixed venous blood is obtained by a cardiac catheter which is passed into the pulmonary artery while the rate of oxygen uptake by the lungs is measured by standard metabolic methods (Courmand *et al.*, 1945; Hamilton, 1945). Cardiac output (CO) is then computed:

$$CO \text{ (in ml/min)} = \frac{\text{ml/min (oxygen uptake)}}{(\text{ml O}_2/\text{ml arterial blood}) - (\text{ml O}_2/\text{ml venous blood})}$$

Errors in the determination of cardiac output by the direct Fick principle may result from anxiety in the patient because of insertion of the catheter and from failure to obtain a true sample of mixed venous blood. If the catheter is in the superior vena cava, the oxygen concentration of the sample will be too high, and if near the coronary sinus, the oxygen concentration will be too low. The most accurate samples are obtained from the right ventricle or pulmonary trunk (Courmand, 1945; Warren *et al.*, 1946; Warren, 1948). When properly performed, this method has a high degree of accuracy (Seely *et al.*, 1950).

Oxygen saturation of blood from various portions of the heart. The oxygen capacity of normal persons is 19.7 volumes per cent. With the person breathing room air, the oxygen content of radial artery blood averages 19.4 volumes per cent; that of the pulmonary artery averages 15.3 volumes per cent. The mean saturation of blood from the inferior vena cava was found to be 83.0 per cent; that from the superior vena cava averaged 76.8 per cent; right atrial blood averaged 79.5 per cent; right ventricular blood averaged 78.5 per cent; pulmonary arterial blood averaged 78 per cent; and the saturation of radial arterial blood averaged 97.3 per cent (Barratt-Boyes and Wood, 1957).

Injection Techniques. Any substance, the concentration of which can be determined

quickly in whole blood, may be used to measure cardiac output. Typical substances are the dyes T1824 and the new Fox Green, concentrated salt solutions, and radioactive substances such as ^{131}I . One of these substances is quickly injected intravenously and the time-course of its concentration in the arterial blood recorded by continuous sampling. The arterial concentration usually rises abruptly to a peak, then declines exponentially. The average concentration in arterial blood is computed from the area under the dye-concentration curve (Emanuel *et al.*, 1957; Goodwin and Sapirstein, 1957; Lacy *et al.*, 1957). Output can also be measured by placing one or more counters directly over various chambers of the heart (Huff *et al.*, 1957; Zipf *et al.*, 1957).

Unfortunately, recirculation begins early on the descending limb so that the latter part of the graph has to be estimated from the slope, of the initial part, thus impairing the accuracy of the determination (Dow, 1956; Schaefer, 1956). Modifications of the injection technique are of assistance in estimating the occurrence of left-to-right and right-to-left shunts and of valvular insufficiency (Crane *et al.*, 1958).

Ballistocardiography. The ballistocardiograph records the oscillations in the longitudinal axis of the body produced by the caudal recoil of the heart as it ejects the blood cephalically, and the cephalic impact delivered to the body as the blood flows through the aortic arch and caudally. The amplitude of these oscillations closely parallels the stroke-volume output of the left ventricle (Nickerson, 1945; Starr, 1945), but is also markedly influenced by the position and the action of the heart (Schaefer, 1956; Reeves *et al.*, 1957). The resonant waves in the aorta (Spencer *et al.*, 1958) may contribute to the waves which are recorded by the ballistocardiograph during the latter part of the heart cycle.

Registration of Arterial Pulses. The stroke-volume of discharge of the left ventricle can also be estimated with fair accuracy by analysis of pressure tracings recorded from the systemic arteries (Hamilton and Remington, 1947; Hamilton, 1950). This method has numerous limitations (Duomarco *et al.*, 1948). A simple nomogram has been devised for estimating the cardiac output from the systolic and diastolic pressures (Jackson, 1955).

Electrokymography. Estimations of stroke-volume

of output of the heart have been made from the pulsations recorded with the electrokymograph. They appear to agree favorably with cardiac output determined simultaneously by the Stewart injection and the direct Fick principles (Ring *et al.*, 1950a, b).

Quantitative Versus Relative Measurements of Cardiac Output. The ballistocardiograph, the methods of registration of arterial pulses and the electrokymograph do not yield direct measures of cardiac output, but only relative changes. The actual output can be calculated only by applying a factor computed from simultaneous comparison with other more direct quantitative methods, such as the direct Fick principle. The ballistocardiograph is also likely to give results having considerable error in the presence of tachycardia. These methods are, however, easy to employ and provide useful information, particularly of the relative changes in output from beat to beat in the same individual. These methods, and particularly the last, give valuable additional information in dynamic disturbances such as coarctation of the aorta, valvular lesions, and ventricular aneurysm.

Normal Values. The standard technique of catheterization of the right atrium or ventricle, gives higher cardiac indices of 2.12 to 4.01 (ave. 3.12 l./min./ M^2 , Dexter *et al.*, 1950). The cardiac output per beat, using this technique, ranges from 53 to 108 with an average of 84 ml. per beat. It should be emphasized that normal figures can be obtained only when the person is in a basal state, as in testing for basal metabolism, i.e., in a post-absorptive state, after a night's rest, without exertion for at least one-half hour prior to the test, having no fever, and being free from anxiety and emotional tension.

Caution in Performing Cardiac Catheterization. The procedure of cardiac catheterization is now often deemed necessary in the physiologic study of disorders of the heart, but is not without some risk. Arrhythmias may be noted in up to 95 per cent of catheterizations, and in one series of 1250 such examinations, there were 7 deaths (Banfield *et al.*, 1950; reviewed by Sculie, 1954).

Output Under Various Physiologic Conditions

Conditions in Which Output is Unchanged. The cardiac output is apparently the same

when the person is asleep as when he is awake and in the horizontal position. It is also unaffected by smoking, by menstruation, or by moderate variations in external temperature but may be increased 5 to 30 per cent at environmental temperatures above 30 C., or by low temperatures if accompanied by shivering.

Increased Output. Cardiac output may be increased 50 to 100 per cent by anxiety and 30 to 40 per cent by eating. The response to eating is diphasic; the output initially increases during eating, returns to normal, and then increases during digestion. Pregnancy (Hamilton, 1949), fever, anemias with a hemoglobin level of less than 7.6 grams, hyperthyroidism, arteriovenous fistula, acidosis, and low oxygen tension in inspired air, i.e., below 10 volumes per cent at atmospheric pressure, are conditions which increase cardiac output as much as 100 per cent. In maximum exercise, the oxygen consumption may be increased twelve-fold and the cardiac output as much as nine-fold. Under these conditions, the heart rates may be increased three-fold and the remaining three-fold increase in output is caused by an increase in stroke volume. The cardiac output is increased by vasodilator drugs, by epinephrine, by atropine (McMichael and Sharpey-Schafer, 1944) and, in certain types of heart failure, by digitalis. Cardiac output is also increased with rapid intravenous infusion. The increase in cardiac output with exercise in normal persons is associated with a decrease in the mean circulation time (Chapman and Fraser, 1954), a rise in systolic and a fall in diastolic pressure, but no significant change in mean aortic pressure (Fraser and Chapman, 1954).

Decreased Output. The cardiac output is decreased 25 to 33 per cent in changing from the recumbent to the vertical position (McMichael and Sharpey-Schafer, 1944). Sudden tachycardias of 200 or more per minute or marked bradycardia, such as is present in heart block, reduce the cardiac output (Katz *et al.*, 1945b). The output is also reduced during inhalation of 100 per cent oxygen (Whitehorn *et al.*, 1946), in myxedema, con-

strictive pericarditis, shock, following myocardial infarction and in many forms of heart failure. In the last, the output may not be abnormally reduced at rest but may not increase to the extent seen in normal persons during exercise. For further discussion of this subject, see pages 223, 233 and 242

Regulation of Cardiac Output

The wide fluctuation in cardiac output under the various conditions noted above are necessary since the rate of oxygen consumption in severe exertion may be increased twelve-fold, whereas only a three-fold increase in oxygen supply could be provided by removing all the oxygen from the blood ordinarily flowing through the tissues, i.e., by increasing the oxygen utilization from 30 to 100 per cent. In general, in normal persons the cardiac output is closely regulated to the need for oxygen, so that the arteriovenous difference in oxygen concentration rises only slightly above the normal value despite large increases in oxygen utilization by the body. Such variations in output, however, involve a complex set of homeostatic integrating (cybernetic) mechanisms.

INTRINSIC CARDIAC MECHANISMS

Ventricular Volume and Stroke-Volume. In man the normal capacity of each ventricle is approximately 140 ml. The normal stroke-volume is approximately 84 ml., but may be increased to about 240 ml. with severe exercise.

Under normal conditions the ventricle is not completely filled, and probably never completely empties itself (Richards, 1949). Nylin (1943) estimated that the residual blood in the entire heart at the end of systole is 400 ml. when the person is recumbent, and 200 ml. when he is erect. The stroke-output of the heart can be increased either by a more complete systolic ejection, as during exercise, or by a greater diastolic filling, as during a "startle reaction" (Rushmer, 1954, 1956a, b).

Effect of Initial Length or Tension of Ventricle. When the arterial pressure and heart rate are kept constant, increasing the systemic central venous pressure produces a progressive increase

in cardiac output per beat up to five-fold (McMichael and Sharpey-Schafer, 1944).

With each increment in initial tension (or length), the vigor of ventricular systole increases, ejection becomes more abrupt and the volume ejected larger. Despite the greater stroke-volume, the volume of blood retained by the ventricle at the end of systole may increase progressively, in other words, the ventricle may empty itself less and less completely with each increase in venous pressure. The myocardial consumption of oxygen increases proportionately to the initial length, the increase, however, is less than the increase in stroke-volume, so that the efficiency of ventricular contraction—the ratio of cardiac work to myocardial consumption of oxygen—increases (Starling and Visscher, 1926-27).

With the heart excised from the pericardium, and with excessive elevations of venous pressure, a degree of initial tension and length is attained at which the heart is no longer able to increase its stroke volume of ejection. With still greater increase in venous pressure, the heart may then reach a state of decompensation in which the cardiac output per beat may be progressively reduced despite a further increase in oxygen consumption. In the normal heart, the rigidity of the pericardium probably prevents such an extreme degree of overdistention, but with chronic congestive failure, overdistention may occur.

Effect of Heart Rate. Increase in heart rate curtails both systole and diastole but preponderantly the latter and, therefore, results in reduction in the time for the ventricular filling.

However, under conditions of maintained venous pressure, the decreasing diastolic time does not reduce cardiac filling since the ventricles relax more rapidly early in diastole, thus allowing them to receive blood from the atria more rapidly (Buckley *et al.*, 1955). Augmentation of cardiac output per minute by acceleration of the heart rate requires a greater increase in myocardial consumption of oxygen than that needed in a similar augmentation in output produced by increasing the stroke-volume (Colin and Steele, 1935).

Effect of Aortic Pressure. Elevation of aortic pressure leads to a momentary reduction in

stroke-volume and, therefore, to a slight systolic residue; this residue added to the normal volume of diastolic inflow leads to greater initial length and to a restoration of the stroke-volume to normal, at which time the cardiac output per minute also returns to normal. Under these conditions, however, the left ventricle is constantly operating at a greater initial diastolic length and with a resulting greater oxygen consumption and a slightly higher left atrial pressure (Katz *et al.*, 1945b).

Effect of Pressure in Pulmonary Trunk. Increase of the pressure in the pulmonary arterial circuit affects the right ventricle in a manner analogous to the effect of elevation of aortic pressure upon the left ventricle. The right ventricular initial volume and tension increase and right atrial pressure rises (Katz *et al.*, 1945b).

Independence of the Two Ventricles. Normally, the average output of each of the two ventricles tends to be adjusted constantly, so as to be equal. If one ventricle lags behind the other, for instance, because of increased resistance to ejection, the pressure in its atrium concurrently rises until the output increases, while the pressure and output in the other atrium and ventricle fall until the outputs of the two ventricles become equal (Berglund, 1954; Schaefer, 1956). The right ventricle, however, is less important than the left, since (a) the right ventricular contractility has been completely abolished by cauterization without causing significant change in either right atrial or pulmonary arterial pressure (Bakov, 1950); (b) dogs, in which the right atrial blood was by-passed directly into the pulmonary trunk, have survived, and (c) patients with constrictive pericarditis have been observed in whom the right ventricle was accomplishing very little work (reviewed by Burchell, 1951).

Effect of Inherent Contractility. During rest in the recumbent position, the heart volume may be large and the stroke-volume output small; with exercise, the stroke-output may greatly increase, yet the diastolic volume of the heart may be no larger or may be even smaller than during rest. These changes cannot be explained solely by Starling's law of the heart (Starling and Visscher, 1926-27); they must represent alterations in the inherent contractility of the ventricles. Such changes in inherent contractility may be brought about indirectly by alterations in heart rate, and directly by variations in influence of sympathetic nerves and of circulating sympathomimetic substances affecting ventricular contractility independently of heart rate. Changes in inherent contractility may affect the cardiac output and the

initial length of the ventricular fibers, even when the venous and aortic pressures remain constant (Green, 1948b).

Ventricular Acceptance (Tone). Changes in ventricular filling without alteration of venous pressure or heart rate are designated as changes in "tone" of the ventricle by Johnson and Katz (1937), and as changes in ventricular acceptance. An increase of ventricular contractility, especially if induced by sympathetic activity, is usually accompanied by a shortening of the duration of systole relative to the length of the cycle and by a more rapid and complete early relaxation (increased acceptance). These two phenomena allow a greater ventricular filling at a given level of atrial pressure and provide another mechanism for augmenting the volume discharged during systole. In a normal person and in unanesthetized animals, changes in inherent contractility and early diastolic relaxation (acceptance) may be much more important than the level of the atrial pressure at the onset of systole in determining the stroke-volume and minute volume-output of the ventricles (Symposium on Regulation of Performance of the Heart, 1955; Rushmer, 1956). For further discussion, see page 185 in section on Nervous and Humoral Regulation of Heart.

EXTRINSIC MECHANICAL FACTORS

Certain mechanical factors extrinsic to the heart modify cardiac output principally by their influence on the volume of blood and on the pressure within the central systemic venous reservoir and the pulmonary venous and left atrial reservoir, respectively.

Normal Values for Central Systemic Venous Pressure. The value for central systemic venous pressure depends, of course, upon the horizontal plane to which zero pressure is referred. Most commonly this has reference to the assumed level of the center of the atrium, *i.e.*, the standard zero reference plane (see page 171). Normal values with this reference plane are 5 to 15 cm. of saline.

The central venous pressure is determined by the volume of blood within the central venous reservoir, *i.e.*, within the superior vena cava, the inferior vena cava above the diaphragm and right atrium, and by the distensibility of this part of the venous system. The quantity of blood within this reservoir is, in turn, dependent upon (a) the

rate at which blood is being removed from the central venous reservoir of the heart, *i.e.*, by the cardiac output, (b) the rate at which blood can return from the peripheral veins to the atrial venous reservoir, and (c) the total blood volume and the capacity of the total vascular system.

Cardiac Output. Other factors remaining constant, an increase in the cardiac output removes blood from the venous side of the circuit and increases the quantity of blood and the pressure in the arterial and capillary portions of the circuit; and conversely, a decrease in the cardiac output per minute decreases the total quantity in the arterial and capillary circuit and increases that in the entire venous system, including the central systemic and pulmonary venous reservoirs. With cessation of cardiac output, such as occurs with ventricular fibrillation or cardiac standstill, the arterial and capillary pressures drop progressively and the central venous pressure rises until the pressures throughout the cardiovascular system become equalized. Under experimental conditions the central systemic venous pressure may rise as much as 3 to 10 mm. of mercury during the establishment of this equilibrium. This pressure is the mean static pressure (Green, 1950b) or the mean circulatory filling pressure (Guyton, 1955). During normal circulation, a pressure equal to the mean static pressure will be present only in the venules or smaller collecting veins.

Difference Between Mean Static Pressure and Central Venous Pressure. The rate of return of blood from the periphery to the central venous reservoir is determined by the frictional resistance between the two points and the pressures existing therein. Increased output of the heart produced by increased contractility *per se* will tend both to lower the central pressure and, simultaneously, to raise the peripheral or mean static pressure and thus increase the rate of return. The first of these will be effective to the point at which the central pressure begins to fall below atmospheric pressure. At that level a flutter-valve effect, at the point of entrance of the veins into the thorax will prevent further lowering of the effective central venous pressure (Guyton, 1935). Presumably, changes in constriction of the larger veins could alter the resistance, as could changes in viscosity of the blood, but as yet effects of measurable magnitude have not been described.

Blood Volume. Increase or decrease of blood volume will alter the mean static pressure and thereby the rate of venous return and the pressure in central venous reservoir. Changes of blood volume result from alterations in the total mass

of red blood cells, the concentration of plasma protein in the blood, and the amount of salt and water retained in the body.

Changes in Vascular Capacity. Central venous pressure apparently can be altered as a result of active changes in the caliber of the entire vascular system, resulting in an increase in pressure exerted by the vascular walls upon the contained blood without a concomitant increase in volume present therein. The portions of the system in which the capacity can be varied include the cardiac chambers themselves, the pulmonary vascular bed, the systemic arteries, the systemic capillaries and the peripheral systemic veins, and such special blood vascular beds as the spleen, the splanchnic viscera and the liver (Ralston *et al.*, 1945-46, Green, 1950b). McMichael (1949) believes this mechanism is controlled by the sympathetic nervous system under the regulation of a center in the nervous system that is closely associated with the vasomotor system regulating arteriolar vasoconstriction. He believes venomotor reflexes are brought into play when there is a need for increased cerebral circulation and, conversely, dilatation of veins and fall in venous pressure result when the pressure in the carotid artery is high and presumably when, therefore, cerebral circulation is adequate. Little (1949) has demonstrated that changes in the vascular capacity are directly related to the tension of the oxygen in the mixed venous blood, *i.e.*, the lower this oxygen tension, the greater is the stimulus to reduction of vascular capacity, and the higher is the pressure in the central venous reservoir.

Posture. The decreased cardiac output (see page 179), on changing from the reclining to the vertical posture, probably results principally from pooling of blood in the more dependent parts of the body which reduces the volume of blood available to fill the central venous reservoirs. This condition is aggravated by quiet standing and is considerably decreased by even mild exercise of the legs. Such muscular activity rhythmically compresses the veins in the legs and, by virtue of the venous valves, reduces the quantity of blood which is stored in the dependent capillaries and veins. The dependent pooling is aggravated by anything which increases the apparent weight of the blood, such as the centrifugal force in the pull-out of an airplane during a dive or sharp turn (Gagge and Shaw, 1950, Green, 1950b). Marked pooling of the blood is also occasionally seen in patients with severe varicose veins.

Respiration. During normal inspiration, the ab-

dominal pressure increases and the intrathoracic pressure decreases. These changes favor return of blood to the systemic central venous reservoir and filling of the right ventricle in diastole, increasing its output. However, simultaneously, the extravascular pressure on the pulmonary capillaries is decreased, thus increasing their capacity and delaying the transmission of the above effects to the left atrium and left ventricle. During expiration the reverse effects occur, decreasing the output of the right ventricle; but because of the decrease in the pulmonary capillary capacity, blood is forced into the left atrium from the lungs, increasing the output of the left ventricle. However, if the respirations are slow enough, the decreased output of the left ventricle seen at the start of inspiration may be counterbalanced; the output of the left ventricle may even increase as the elevated output of the right ventricle becomes transported through the lungs to effect the left atrial and left ventricular diastolic pressure (Lauson *et al.*, 1946; Seely, 1948).

In artificial respiration with application of positive pressure, the net filling pressure of the right ventricle is decreased in inspiration during the phase of rising pressure and increased in expiration during the phase of decreasing pressure. It is concluded that the effect on average cardiac output is minimal with a breathing mask having intermittent positive-pressure in which the mask-pressure gradually increases during inspiration and rapidly falls at the end of inspiration, and the mean mask-pressure during expiration is as near atmospheric pressure as possible (Courmand *et al.*, 1948). Venous return by way of the superior vena cava is greater with attenuating positive-negative than with alternating positive-zero assisted breathing (Gregg, 1955).

When dogs breathed against a constant positive pressure of 16 cm. of saline, they showed a decrease of cardiac output, an increase in central systemic venous pressure and a decrease in the gradient from peripheral to central veins. When they breathed against a constant negative pressure of 16 cm. of saline, the central venous pressure fell and the gradient from peripheral to central veins increased, probably because of collapse of the veins as they entered the thorax while the cardiac output remained approximately normal (Holt, 1944).

Circulation Time. Circulation time is the elapsed time between the injection of a substance at one point in the circulation and its arrival at another. Most commonly the time

is measured from the cubital vein to the tongue, using a substance which gives a taste sensation. The circulation time is shortened with increased cardiac output and prolonged with decreased output, or with the sluggish

velocity of flow associated with dilatation of any of the cardiac chambers (with increased systolic residual volume) or of the pulmonary vascular bed (Gernandt and Nylin, 1946, Chapman and Fraser, 1954).

4. WORK OF THE HEART

The mechanical work done by the heart per beat is roughly the product of the volume of blood ejected per beat times the average pressure against which the blood is ejected, i.e., the average or mean aortic pressure during systole.

This computation, however, measures only the pressure-energy of the heart. Some additional energy is required to give the blood its initial velocity. The velocity or kinetic energy for the work of the human left ventricle is 0.25 to 2.0 per cent

of the total, while the kinetic energy for the right ventricle is 2.4 to 12.5 per cent of the total (Pree *et al.*, 1949). The kinetic energy is converted to pressure energy as the velocity of blood flow slows during diastole, therefore, by multiplying the stroke-volume of discharge by the average aortic pressure throughout the heart cycle, one may obtain a reasonably close approximation to the total work per beat. The heart work per minute, of course, is the heart work per beat times the number of heart beats per minute.

5. NERVOUS AND HUMORAL REGULATION OF HEART

Nerve Supply

Sympathetic Fibers. Preganglionic sympathetic fibers, capable of affecting the heart, leave the spinal cord by way of the upper five thoracic roots. The synapses are found in the corresponding paravertebral and the stellate ganglia and the postganglionic fibers then proceed to the heart by way of the cardiac nerves. They are distributed to the S-A and A-V nodes, conduction tissue, atrial and ventricular musculature and coronary arteries.

The effect of sympathetic nerve stimulation is mediated by an epinephrine-like substance released at the sympathetic nerve terminals (Loewi and Navratil, 1926, Cannon and Bacq, 1931).

It was first thought that the mediator was epinephrine (Lewandowsky, 1899; Elliott, 1903; Langley, 1921). Subsequently, Cannon and Rosenblueth (1937) proposed that two "sympathins" are released as a result of stimulation of the sympathetic nerves (reviewed by Sheehan, 1936). However, later studies indicate that adrenalin (norepinephrine) is the mediator (Outschorn and Vogt, 1952; Youmans *et al.*, 1955, von Euler, 1956).

Parasympathetic Fibers. Parasympathetic

preganglionic fibers are conveyed to the heart in the vagi. The synapses with the postganglionic fibers are found in the intrinsic cardiac ganglia. Postganglionic fibers of parasympathetic origin are distributed to both the S-A and A-V nodes, to the upper portion of the special conduction tissue, and to the atrial myocardial fibers, but none are known to be distributed to the ventricular myocardium (Garrey and Ashman, 1931). Langley (1921) noted that pilocarpine causes effects similar to those produced by stimulation of fibers in the cranial and sacral portions of the autonomic outflow from the central nervous system, and called these the parasympathetic nervous system. Loewi (1926) discovered that stimulation of the vagus released a substance into the fluid perfusing the heart which had vagus-like effects when re-introduced into an isolated perfused heart. Subsequent studies demonstrated that this substance was acetylcholine. (See Abdon, 1945, for review.)

Regulation of Heart Rate (Chronotropic Regulation)

Frequency of Initiation of Impulses in S-A and A-V Nodes. The sinoatrial node is more strongly controlled by the autonomic nervous

system than any other region of the heart (Schaefer, 1956). Sympathetic nerve impulses cause the sinoatrial node to initiate cardiac beats more frequently. Also both epinephrine and arterenol applied to the sinoatrial region produce marked increases in the rate of initiation of impulses in the sinoatrial node; the latter is slightly more potent than the former (Brooks *et al.*, 1955). Parasympathetic impulses cause the sinoatrial node to initiate cardiac beats less frequently. Vagal stimulation decreases the slope of the slow phase of the depolarization of the pacemaker tissue (see page 167) and may even hold the potential constant, thus serving to prolong or even prevent the spontaneous depolarization of the pacemaker tissues which is essential for the initiation of the cardiac impulse (Brooks *et al.*, 1955).

In the perfused heart the frequency of initiation of cardiac impulses in the S-A node is increased by warming, by increased pH and by increased concentration of calcium ions and is decreased by cooling, by decreased pH, and by increased concentration of potassium ions.

When the S-A node is depressed, the A-V node often serves as the pacemaker. The frequency with which it generates impulses is affected in a manner similar to that of the S-A node, but to a lesser extent by the above-mentioned nerves. When the A-V node served as the pacemaker, owing to depression of the S-A node, stimulation of the vagi frequently caused a shift of the pacemaker back to the S-A node.

Stimulation of the sympathetic nerve may increase the rhythmicity of the A-V node to the point where it becomes the pacemaker. When the A-V node serves as pacemaker, impulses go forward through the special conduction system to excite the ventricle, and backward to the atrium and to the S-A node.

Regulation of Excitability (Bathmotropic Regulation)

Duration of Refractory Period of Atrial and Ventricular Myocardium. Sympathetic impulses shorten the duration of the contraction and the refractory periods of atrial and ventricular systole. Brooks and associates (1955) stated that sympathetic nerve stimulation produces only slight and inconsistent alterations of the duration of the total refrac-

tory period but that injections of epinephrine and arterenol cause a small degree of shortening of the absolute and relative refractory periods. Transmembrane potential recorded from the atria indicates that sympathetic stimulation is accompanied by an increased rate of repolarization and of shortening of the duration of the total action-potential.

Parasympathetic impulses have no demonstrable effect on the ventricle. If the rate is kept constant, vagal stimulation abbreviates the refractory period of the atria. The absolute refractory period is shortened to a greater extent than the relative refractory period. This change is accompanied by a dramatic abbreviation of the first half of the repolarization portion of the transmembrane action-potential (Brooks *et al.*, 1955). Atrial fibrillation occurs more readily during parasympathetic activity, especially in association with thyrotoxicosis; this may result from shortening of the refractory period.

Effects on Threshold. During vagal stimulation or the injection of acetylcholine, the excitability of the atrial tissue of the turtle is decreased, i.e., more energy is required to excite the tissue. This effect parallels that of the vagus and of acetylcholine on atrial contractility. In the mammalian atrium, however, neither maximal stimulation of the vagi or of the sympathetic nerves, nor injections of epinephrine or arterenol have any effect on the diastolic level of excitability (Brooks *et al.*, 1955).

Regulation of Rate of Conduction (Dromotropic Regulation)

Conduction Tissue. Increased activity of the sympathetic nerves and injections of arterenol, and especially of epinephrine (Brooks *et al.*, 1955), increase the velocity of conduction from atrium to ventricle, that is, shorten the atrioventricular interval ($A-V_c$ interval in pulse curves and the P-Q interval in the electrocardiogram). The refractory period of the conduction tissue is shortened by sympathetic impulses in proportion to the increase in heart rate. The left sympathetic fibers appear to have greater effect on the A-V node than do the right.

Parasympathetic excitation slows the rate

of conduction through the A-V node (incomplete heart block) and increases the length of the refractory period (partial heart block). The latter effect results in the occurrence of a 2:1, 3:1 or higher degree of block, *i.e.*, only every other or every third beat is transmitted to the ventricle (page 204). Strong excitation of the vagal fibers, particularly of the right vagus, may cause complete cessation of atrial contractions, but after a short period of time, ventricular contractions may occur at a slow rate. The ventricle is then said to "escape" from the vagal inhibition, the impulses arising from idioventricular centers. This condition is designated as complete heart block with idioventricular rhythm (page 204). Vagal impulses have no effect on the conduction of the impulse through the distal special conducting system or through the myocardium but may depress conduction in the common bundle or its proximal branches.

Atrial and Ventricular Myocardium. The velocity of conduction of the impulse and the resting excitability is increased in both atrium and ventricle by sympathetic nerve stimulation (reviewed by Gregg, 1953).

Regulation of Atrial and Ventricular Contractility (Inotropic Regulation)

It has been thought that cardiac output was regulated solely by the pressure in the central venous reservoir, the output then being determined through the operation of the Starling mechanism (pages 179 and 180). More recent studies suggest that the output of the heart may also be regulated by nervous and humoral mechanisms affecting the contractility of the atrial and ventricular myocardium.

Excitation of the vagus causes a decrease in the contractility of the atrial tissue; if the excitation is strong enough, atrial contraction may be abolished entirely. Provided that the ventricular contractions are artificially maintained at a constant rate, no effect is noted on ventricular contractility during vagal stimulation (Denison and Green, 1958). However, in the intact heart, vagal stimulation causes cardiac slowing with resulting greater diastolic filling and, therefore, greater stroke-volume. Acetylcholine is said to have a direct stimulating effect on the ventricle which may be caused by release of an epineph-

rine-like substance but it has no such effect when injected directly into a coronary artery (Denison and Green, 1958).

Sympathetic stimulation apparently increases the vigor of myocardial contraction for a given central venous pressure, *i.e.*, for a given initial length, and results in a more abrupt contraction, a more nearly complete ejection, shortening of systole and more rapid relaxation. Similar effects follow injections of epinephrine, arterenol (norepinephrine) and isoproterenol (Anzola and Rushmer, 1956, Randall and Rohse, 1956, Rushmer, 1956, Denison and Green, 1958). The net effect is to increase ventricular filling by increasing the ventricular acceptance of blood (see page 181). Sympathetic stimulation and epinephrine appear to increase consumption of cardiac oxygen more than they increase the work of the heart, in other words, they appear to decrease the efficiency of myocardial contraction (Raab and Lepeschkin, 1950, Schaefer, 1956). An epinephrine-like substance can be extracted from normal cardiac muscle (von Euler, 1946). This substance is present in increased amounts after prolonged sympathetic stimulation and decreased after sympathectomy (Raab and Lepeschkin, 1950). Adrenergic blocking drugs, such as lhdar, Dibenamine, Priscoline and 933F,* appear to protect the heart against excessive concentrations of these epinephrine-like substances (Raab and Humphreys, 1946). A similar protective effect is exerted by nitroglycerine (Raab and Lepeschkin, 1950). The liver seems to be essential for maintenance of normal cardiac contraction, but it is not known whether it supplies an essential hormone or metabolite or removes some depressant metabolic product (Poli and Rossi, 1950).

Central Mechanisms for Controlling Sympathetic and Parasympathetic Nerve Activity

Sympathetic Cardio-accelerator and Vaso-constrictor Centers. Paired bilateral neurons, connected with the sympathetic fibers to the heart, are located in the reticular substance of the medulla. Electrical excitation of these neurons increases the intensity of the impulses to the heart by way of the sympathetic nerve

* lhdar is available from Hoffmann-LaRoche, Inc., Nutley, N. J., Dibenamine from Smith, Kline and French Laboratories, Philadelphia, Pa.; Priscoline from Ciba Pharmaceutical Products, Inc., Summit, N.J., and 933F was supplied by Dr. Louis Goodman, then Professor of Pharmacology and Physiology, University of Vermont, Burlington, Vt.

fibers and causes increase of heart rate. This medullary center is designated the *cardio-accelerator center*. Excitation of a closely related center, the *sympathetic vasoconstrictor center*, causes arteriolar vasoconstriction which, in turn, causes elevation of arterial pressure. Stimulation of the latter center probably also causes constriction of the vascular blood reservoirs and elevation of venous pressure. Both the accelerator and constrictor sympathetic centers act more or less concomitantly.

Parasympathetic Cardioinhibitory Centers. Located in the vagal nuclei in the medulla, close to the above-mentioned sympathetic centers, is a paired parasympathetic center, excitation of which increases the intensity of the impulses in the vagal fibers, causing slowing of the heart rate.

Cardiovascular Regulatory Center. Grouped together, the accelerator, the constrictor, and the vagal centers may be designated the cardiovascular regulatory center. In general, the sympathetic and parasympathetic centers operate reciprocally; anything that increases the activity of one tends to inhibit the activity of the other (Wang and Borison, 1947). These centers are tonically active at all times, that is, are continually sending out impulses over their respective pathways. As a result, the heart rate may be speeded by increasing sympathetic activity or by decreasing parasympathetic activity. At normal resting heart rates, the vagal fibers are active. Increase of heart rate to about 120 beats per minute is accomplished mainly by decreasing the vagal activity. Rates of 120 per minute can, for instance, be induced by blocking the vagal impulses by large doses of atropine. In order to increase the heart rate to 150, and especially to a rate over 150 per minute, it is also necessary to have augmented sympathetic nerve activity.

Factors Affecting Medullary Centers. (Direct Effects of Change in Composition of Blood.) Increase of carbon dioxide tension, decrease of oxygen tension, or decreased pH from the normal level of the blood flowing by the medullary cardiovascular regulatory center tends to cause speeding of the heart by inhibiting the vagal

center and exciting the cardio-accelerator and vasoconstrictor centers. The net effect is a rise in both arterial and central venous pressures and an increase in cardiac output. To some extent, reverse changes in the circulatory system are produced by decreased tension of CO_2 , increased tension of O_2 , or increased pH.

Reflex Effects from Chemoreceptors. The carotid bodies located near the point of origin of the internal carotid arteries and the aortic bodies located near the arch of the aorta are irrigated by the systemic arterial blood. Sensory endings are located in these structures which are excited by increase of CO_2 tension or by decrease of O_2 tension or of pH. Impulses discharged from these sensory endings are conveyed, respectively, by the ninth and tenth cranial nerves to the above-mentioned medullary centers where they augment the effects of the changes in blood composition.

Reflex Effects from Pressoreceptors. Sensory endings are located in the walls of each common carotid artery near the origin of the internal carotid artery and in the arch of the aorta. These endings are excited in proportion to the level of the arterial blood pressure. Elevation of arterial pressure leads to increased intensity of the afferent nerve discharges which are conveyed from the sensory endings to the medulla by way of the ninth and tenth cranial nerves, respectively. These impulses in turn cause inhibition of the cardio-accelerator and vasoconstrictor centers and excitation of the cardioinhibitory (vagal) center. The afferent fibers are designated the moderator or depressor fibers, since electrical excitation of them causes a fall of arterial pressure and slowing of the heart and since cutting the fibers causes permanent neurogenic hypertension and cardiac acceleration. Decrease of pressure in the carotid sinus results in a diminished discharge of inhibitory impulses to the medulla. As a consequence, there is decreased discharge of impulses by way of the vagi and an increased discharge of sympathetic impulses to the heart and to the arterioles throughout most of the systemic vasculature (except for the brain and heart). The effects on the nerves to the arterioles are much greater than those to the heart, leading to a rise of arterial pressure with only a slight increase in force of ventricular contraction (Cotten and Moran, 1958). The normal moderating action of these receptors, in response to hypertension, may be rendered less effective by the presence of circulating arterenol or epinephrine (Rushmer, 1956b). It is possible that other circulating

hypertensive substances may modify the action of the pressoreceptors in essential hypertension also.

Bainbridge Reflex. Pressure receptors are also thought to be present in the venae cavae and pulmonary veins, and are stimulated by an increase of pressure in these vessels. Increase in then afferent impulses causes cardiac acceleration. This effect is called the *Bainbridge reflex* (Bainbridge, 1915). Other investigators, however, report that stimulation of stretch-receptors in the right atrium and pulmonary trunk reflexly induces cardiac slowing (reviewed by Burchell, 1951).

Coronary "Chemoreflex" (Jarish von Bezold Reflex). Receptors are located in the heart, particularly in the region supplied by the circumflex branch of the left coronary artery. These receptors are stimulated by drugs, such as the veratrum group. The afferent impulses are conveyed by way of the vagi to the medulla where they enhance the vagal discharge and probably suppress the sympathetic discharge to the heart, causing cardiac slowing. These afferent impulses also suppress the activity of the sympathetic vasoconstrictor center, thereby inducing vasodilatation. Both mechanisms lead to a lowering of arterial pressure. The normal physiologic function of this reflex is unknown. The physiologic behavior of this reflex has been reviewed recently by Dawes (1954), and data on the participation of the reflex in the anti-hypertensive actions of

the veratrum drugs are given by Green (1954).

Other Regions in Nervous System Affecting Medullary Centers. Nervous impulses from the hypothalamic centers integrate the activity of the medullary cardiovascular regulatory center in the regulation of body temperature and in emotional reactions, e.g., tachycardia associated with anxiety. Impulses from the motor areas of the cerebral cortex (Green and Hoff, 1937) and probably also impulses from contracting muscles alter the activity of the medullary centers, so as to improve the blood flow in the skeletal muscles during physical exertion. The medullary centers are also affected by impulses from the respiratory centers, the heart rate tending to vary with respiration; by afferent impulses in the minor splanchnic nerves, stimulation causing a fall in arterial pressure, and by afferent fibers in many sensory nerves, probably pain fibers, electrical stimulation causing a rise of arterial pressure.

Influence of Potassium and Calcium. Increase in concentration of potassium ions tends to slow the heart and to cause marked slowing of intraventricular conduction and decreased contractility. Increase in concentration of calcium ions causes speeding and increased contractility; excessive concentrations of calcium prevent full relaxation of the ventricles during diastole (Brooks *et al.*, 1955). (See also page 233.)

6. MYOCARDIAL METABOLISM AND CORONARY CIRCULATION

It is extremely difficult to secure exact figures for the coronary blood flow, and particularly for myocardial metabolism with the heart normally functioning *in situ*. Most data have been obtained from isolated perfused hearts, or at best by simultaneous measurement of the composition and rate of coronary artery inflow and of the composition of the coronary sinus venous outflow of blood, in the animal with chest cavity exposed. A technique has been developed for estimating coronary flow from the rate of uptake of nitrous oxide by the myocardium, by measurement of successive differences in concentration of this substance in the systemic arterial and coronary sinus venous blood, while inhaling low concentrations of the gas. This method gives results which, fortunately, are comparable with the direct methods and makes possible, for the first time, extension of the studies to man (Bing *et al.*,

1954). From simultaneous recordings of coronary artery inflow using the rotameter and the nitrous oxide method, Cregg and associates (1951) concluded that the latter has an average accuracy of ± 12.4 per cent (extremes $+21$ to -22 per cent).

Myocardial Metabolism

When the concentration of sugar in the blood is high, the myocardial respiratory quotient approaches 1.0, suggesting that carbohydrate serves as the primary source of fuel. Goodale and associates (1950) found in man a normal nonfasting respiratory quotient of 0.89 to 0.93. Oxidation of glucose, lactate and pyruvate, computed from arteriovenous differences in concentration, accounted for 90 to 100 per cent of the oxygen uptake meas-

ured simultaneously. The amount of these substances extracted from the blood by the myocardium is in direct relation to the arterial concentration of each substance independently of that of the others. Glucose is not utilized below a mean threshold of 54 mg. per 100 ml. (Goodale and Hackel, 1953, Schaefer, 1956). As the level of blood sugar falls, the respiratory quotient shifts towards 0.7 (Goodale *et al.*, 1950). Under the latter conditions, myocardial fat, blood fatty acids or ketones may be consumed (Pearson *et al.*, 1949a, b). Amino acids apparently do not serve as a substitute fuel (Gruickshank, 1936).

Both in patients with diabetes mellitus and in dogs with alloxan diabetes, utilization of myocardial glucose is diminished relative to the normal heart, usage of lactate is markedly decreased and that of pyruvate slightly diminished, while ketones and fatty acids are extracted at increased rates (Ungar *et al.*, 1955). In the presence of severe diabetes, the myocardial respiratory quotient may also approach 0.7, with glucose oxidation virtually absent. Addition of insulin raises the respiratory quotient to 1.0 without changing the oxygen uptake.

Myocardial glycogen is reduced slightly (20 per cent) by lowering of blood glucose levels. When epinephrine is added, myocardial glycogen rapidly disappears. After such reduction, glycogen levels can be restored by addition of glucose, but not of lactic acid to the perfusate. The concentration of myocardial glycogen varies with blood ketone levels, but not with blood glycogen or lactic acid levels, in animals that have first been fasted, then given butyric acid or glucose in the diet. The concentration of myocardial glycogen invariably increases from a normal level of 0.6 to the order of 1.25 gm. per 100 gm. of muscle in diabetes mellitus and is reduced by addition of insulin, whereas administration of insulin to normal animals increases the concentration of myocardial glycogen (Cruickshank, 1936). The glycogen concentration in mammalian hearts is reduced following anoxia, burns, or histamine intoxication, and in shock (reviewed by Fishman and Courmand, 1953).

The normal heart consumes considerable quantities of both lactate and acetate. During gradual reduction of its oxygen supply, the heart continues to utilize glucose and lactate. Failure suddenly occurs with oxygen tensions of 15 to 30 mm. of mercury, at which time the heart begins

converting glucose to lactic acid, with outward instead of inward diffusion of the latter. Under these conditions, survival is prolonged by elevation of the concentration of blood glucose but not by increase of lactic acid levels (Bogue *et al.*, 1938).

Phosphorus metabolism appears to parallel that of skeletal muscle, adenosine triphosphoric acid and phosphocreatine (phosphogen) serving as phosphorus donors, and adenylic acid and creatine as phosphorus acceptors (Wollenberger, 1949). In asphyxia and aglycemia a marked decrease in phosphogen occurs in ventricular muscle (Cruickshank, 1936). Digitalis and related compounds, cholesterol, estone, testosterone, and alpha tocopherol (vitamin E) protect the myocardium against anaerobic breakdown of coenzyme I (Govier *et al.*, 1946).

Normal Values for Consumption of Myocardial Oxygen. The difference in oxygen concentration between systemic arterial and coronary sinus venous blood is larger than the arteriovenous difference for any other organ under resting conditions, and is of the order of 11 to 19 ml. of oxygen per 100 ml. of blood flow. This figure, combined with that for the rate of coronary blood flow of 70 ml. per minute, gives an oxygen uptake by the myocardium of the order of 7 to 10 ml. per minute per 100 gm. of myocardial weight for man and 9 to 24 ml. per 100 gm. per minute for dogs (Spencer *et al.*, 1950), which is exceeded only by the kidneys (18 ml. per minute per 100 gm.) and possibly by the thyroid gland. Under resting conditions, the heart uses about 9 per cent of the total oxygen consumed by the body.

Coronary Blood Flow

Normal Values. In dogs the heart weighs approximately 7.5 gm. per kilogram of body weight. In man the heart appears to be relatively slightly smaller, the figure frequently quoted being 300 grams for a man weighing 60 kilograms or 5 grams per kilogram. The most satisfactory estimates at present place the normal flow at 55 to 70 ml. per minute per 100 gm. of heart weight, or approximately 120 ml. per minute per square meter of surface area; that is, under resting conditions the total coronary blood flow is of the order of

4 to 5 per cent of the cardiac output per minute.

Phasic Coronary Blood Flow. The flow of blood into the coronary artery at each instant in the heart cycle may be recorded with a suitable flowmeter (Gregg and Green, 1940; Denison *et al.*, 1956). Figures V-7 and V-8 are records obtained with such a meter.

The tension developed in the ventricular walls during systole produces strong extravascular compression of the coronary blood vessels, with a consequent increase in the resistance to flow through these vessels. As the myocardium contracts, it also squeezes blood out of the small vessels and back into the coronary arteries. These two factors cause the rapid systolic reduction in inflow (Jochim, 1940). At the same time, of course, blood is also "massaged" forward into the coronary sinus. The sharp rise in flow at the beginning of ventricular ejection is caused primarily by the uptake of blood in the superficial coronary vessels with the rise in aortic pressure. The initial rapid inflow of blood into the coronary artery with the onset of isometric relaxation is in part the result of the uptake of blood to fill the previously compressed capillaries.

The instantaneous blood flow through the myocardium can be computed accurately only during the latter part of systole and at the end of diastole. The effect of drugs on the portions of the coronary vessels which regulate coronary blood flow can be estimated best by measuring the coronary blood flow at the end of diastole (Katz *et al.*, 1938; Gregg and Green, 1940) although measurements of mean flow give a fairly close approximation to this figure (Denison and Green, 1958).

The phasic flow in the circumflex branch of the left coronary artery is essentially similar to that described above for the anterior descending branch. The right coronary artery flow (see Figure V-7) undergoes changes qualitatively similar to those in the left coronary artery throughout the heart cycle, but the reduction in flow in systole is proportionately much less, because of the lower intramyocardial tension in the right ventricular wall. The lower intramyocardial systolic tension is associated with lesser systolic intraventricular tension in the right as compared with the left ventricle (Gregg *et al.*, 1943; Gregg, 1950).

In the case of the left ventricle, increased

left ventricular work resulting from a rise of aortic pressure is compensated to some extent by the rising head of pressure in the coronary arteries supplying this ventricle. On the other hand, when the pressure in the pulmonary trunk rises, a compensatory rise of pressure does not take place in the coronary artery supplying the right ventricle. This disproportion contributes to right ventricular failure in the presence of pulmonary arterial hypertension (Salisbury, 1955).

Relation of Coronary Blood Flow to Myocardial Metabolism. Ordinarily the venous blood returning from most regions of the body has an oxygen concentration of around 14 volumes per 100 ml. blood, *i.e.*, the oxygen

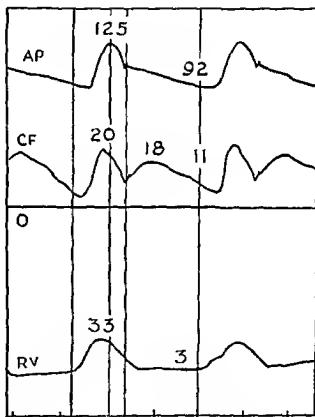


Figure V-7. An example of flow into the right coronary artery measured with the orifice meter for "instantaneous rate of flow." In top curve, AP indicates aortic pressure and figures represent maximum and minimum pressures in mm. Hg. In middle curve, CF indicates coronary flow and figures represent rate of flow in ml./min. at the indicated points. The O line indicates the position which the top of the flow curve would occupy at zero flow. In the bottom curve, RV indicates right intraventricular pressure and figures represent the maximum and minimum pressures in mm. Hg. (Reproduced from Gregg, 1950, by courtesy of Lea and Febiger, Philadelphia.)

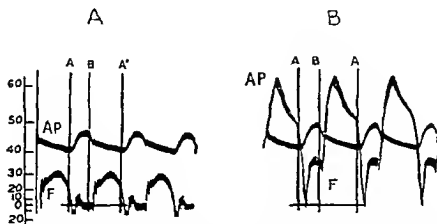


Figure V-8. Segments of records showing effects of asphyxia upon the left coronary blood flow. AP, aortic pressure; F, blood flow in descending ramus of left coronary artery; scale at left gives rate of flow in ml./min.; figures below zero are for backflow. The studies were performed upon a dog with chest opened, under morphine and sodium barbital anaesthesia. Asphyxia was produced by stopping the artificial respiration. During the control periods (left-hand record A) aortic pressure was 93/52, the heart rate was 135/min and the average coronary flow was 17.5 ml./min. At the height of the asphyxial effect (right-hand record B), 1 min 40 sec. after onset of asphyxia, the aortic pressure was 104/56, the heart rate was 121/min, and the average coronary flow was 45.8 ml./min. (Reproduced with modifications, from Green and Wegria, 1942.)

utilization amounts to approximately 30 per cent. The coronary sinus blood has an oxygen concentration of about 6 to 8 volumes per 100 ml. of blood, indicating an oxygen utilization of about 65 per cent. It is, therefore, obvious that increased metabolic demands by the myocardium must be met principally by an increased coronary blood flow rather than an increase in the oxygen utilization.

The coronary blood flow under varying conditions increases approximately in proportion to the cardiac work and the intraventricular pressure whether or not accompanied by cardiac acceleration. This increase is the result of dilatation of the arterioles and small terminal arteries which regulate the coronary blood flow (Gregg, 1946). The degree of coronary arteriolar dilatation is most closely related to the oxygen concentration of the myocardium since the coronary blood flow increases markedly during reduction of the oxygen concentration of the inspired air (Figure V-8), or intracoronary injection of sodium cyanide; and after ischemia of as short a duration as 5 seconds, but is not influenced by an increase in the concentration of carbon diox-

ide in the inspired air (Green and Wegria, 1942, Katz *et al.*, 1945a, 1955; Foltz *et al.*, 1950). The magnitude of the vasodilation is related to the degree of lowering of the oxygen saturation of the coronary sinus blood (Berne *et al.*, 1957). However, no evidence has been found to indicate the presence of any vasoactive substance in the coronary sinus blood (Jelliffe *et al.*, 1957).

Nervous and Chemical Control of Coronary Blood Flow. Stimulation of the cardiac sympathetic nerves (Figure V-9) and intracoronary arterial injections of arterenol (nor-epinephrine), epinephrine (methylarterenol), and isoproterenol (isopropylarterenol) all cause an increase in the mean coronary flow and in the phasic flow at the end of diastole, indicating coronary arteriolar dilatation. They all also cause shortening of systole, a reduction of flow during systole and a greater reduction of inflow, and often the appearance of back flow during isometric contraction, suggestive of increased vigor of myocardial contraction; and a more rapid inflow in early diastole, suggestive of more rapid relaxation of the ventricle in early diastole.

Nothing suggestive of coronary arteriolar constriction is noted in blood-perfused mammalian hearts with any strength of adrenergic stimulus or with any dose of the adrenergic substances (Denison and Green, 1958).

By occluding the inflow to a coronary artery while recording the pressure downstream from the occlusion, it is possible to record the peripheral coronary pressure. These curves (Figure V-10) show a rise in pressure beginning with the onset of isometric contraction and a decline beginning with the onset of protodiastole. The steepness and magnitude of the rise and fall are increased and the duration of the elevated portion shortened by sympathetic nerve stimulation and by all three adrenergic substances. The myocardial compression, which is responsible for the rise in pressure, has been thought by some investigators to improve coronary flow, but the consensus is that it serves rather to throttle flow (reviewed by Gregg, 1955). However, the greater systolic compression induced by adrenergic stimulation is usually accompanied by a more abrupt early diastolic relaxation, so that there is little over-all effect of changes of contraction on coronary flow (Denison and Green, 1958).

Stimulation of the vagus caused no significant change in the phasic flow at the end of

diastole despite considerable cardiac slowing. Neither constrictor nor dilator fibers were demonstrated in the vagus of the dog. The effects on mean flow were largely the result of changes in the relative duration of diastole per heart beat (Figure V-11) and on the level of the mean diastolic pressure. Injections of acetylcholine into the left descending coronary artery, in contrast to vagal stimulation, caused changes in flow similar to those induced by the nitrites, indicating a definite coronary arteriolar dilator effect (Schreiner *et al.*, 1957; Denison and Green, 1958).

Under the influence of sympathetic stimulation, the coronary blood flow increased less than did the oxygen uptake; as a result, the arteriovenous difference in oxygen concentration was increased, and the increase in total oxygen uptake was relatively greater than the increase in cardiac work, indicating that sympathetic stimulation decreased myocardial efficiency. On the contrary, parasympathetic stimulation decreased the oxygen uptake in proportion to the work of the heart and, therefore, may be said to have increased myocardial efficiency (Gollwitzer-Meier and Kroetz, 1938; Raab and Lepeschkin, 1950).

Reports have appeared at various times suggesting that coronary flow can be influenced reflexly by impulses arising in various parts of the body (Gilbert *et al.*, 1940), especially the abdominal viscera and gallbladder, but consider-

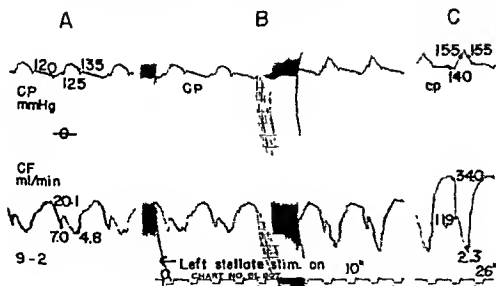


Figure V-9. Coronary perfusion pressure, CP, and coronary flow curves, CF, during a control period (segments A) and during stimulation of the left stellate ganglion (segments B and C). Figures adjacent to the curves are rates of flow in ml. per minute and pressures in mm. Hg. (Reproduced from Denison and Green, 1958.)

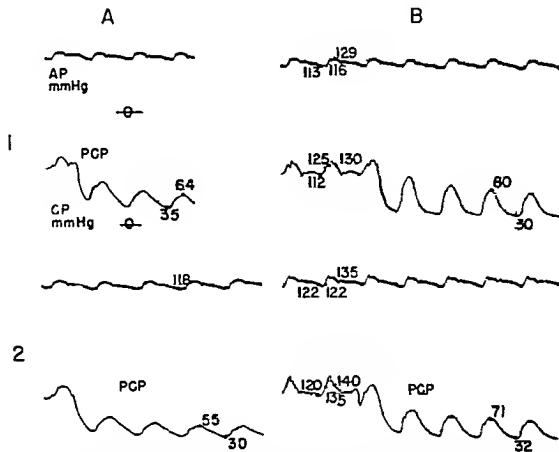


Figure V-10. Curves of peripheral coronary pressure illustrating effects of intra-arterial injections of $1\mu\text{g}$ of arterenol (1) and of stimulation of the cardiac sympathetic nerves (2). Segments A, control, segments B, experimental effects. In each segment, the upper curve, AP, is the aortic pressure recorded by a catheter inserted into the aorta by way of the brachial artery, and the lower curve, PCP, is a curve of the lateral pressure in the coronary artery. In the first portion of each segment, the curve PCP records the normal pressure in the coronary artery which is essentially similar to that in the aorta. After the first 1 or 2 cycles, the coronary artery flow is occluded upstream from the pressure gauge so that the gauge records the peripheral pressure in the coronary artery. This pressure drops abruptly, then rises and falls with each cardiac cycle. The figures adjacent to the curves are the pressures in mm. Hg. (Reproduced from Demson *et al.*, 1956.)

able doubt still remains regarding the importance of such reflexes (Fishman and Courmand, 1953).

Myocardial Capillaries. The myocardial capillaries run parallel to the muscle fibers, and are of such number that normally each muscle fiber lies in direct contact with one or more capillaries. Hypertrophy, developing because of cardiac disease, causes enlargement of the muscle fibers without increase in the capillaries and, as a consequence, the capillary supply per unit volume of heart muscle is decreased (Cregg, 1946).

Distribution of Coronary Blood Supply. There are three distinct patterns of distribu-

tion of the coronary arteries. In about one-half of all human hearts, the right coronary artery is dominant, *i.e.*, the right coronary artery supplies all of the right ventricle, a large part of the posterior wall of the left ventricle, and the posterior half of the intra-ventricular septum. In about one-fifth of all hearts, the left coronary artery is dominant, supplying all of the left ventricle, the right ventricle in its posterior aspect, the region of the pulmonary conus, and the entire intra-ventricular septum. The remainder of all hearts have a balanced circulation, each ventricle receiving its blood supply from its corresponding artery; the posterior half of the intra-

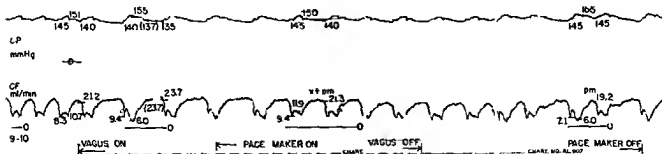


Figure V-11. Curves illustrating lack of effect of the vagus on the coronary arterioles. Upper curve, CP, records the lateral pressure in the coronary artery; the lower curve, CF, gives the rate of flow from moment to moment in the descending ramus of the left coronary artery. The figures adjacent to the curves give the pressures in mm. Hg and the rates of flow in ml. per minute. The lines with the zeros adjacent to them are the points assumed by the recorders at zero pressure and zero flow, respectively. In this experiment, first a control was run, then, while stimulating the vagus nerve, an attempt was made to drive the heart at approximately the control rate by means of an artificial pacemaker applied to the right auricular appendage. Stimulation of the vagus was then discontinued and finally the pacemaker was stopped. As can be seen, neither the flow at the end of diastole, nor the flow at a point in the slower heart cycles (corresponding to the same time-interval as the end of diastole in the control beats) showed any significant change in flow or pressure as compared to the control. (Reproduced from Denison *et al.*, 1956)

ventricular septum is supplied by the right artery and the anterior half by the left artery (Cregg, 1950).

In dogs the dominant blood supply to the sinoatrial node is from the dorsal right atrial branch of the right coronary artery, but the node may receive blood also from the left coronary artery and the right internal mammary artery by way of its pericardiophrenic branch (Halpern, 1954).

Collateral Communications. Small arterial communications exist between the smaller branches of the coronary arteries, between the main coronary arteries, and to some extent between the coronary arteries and the extra-cardiac structures. These communications are quite small, of the order of 40 microns (Schlesinger, 1938; Baroldi *et al.*, 1956).

In the dog the communications between the main coronary arteries are principally superficial (Bobb *et al.*, 1948). In the young pig, as in the young dog, the intercoronary anastomoses are quite small (Eckstein, 1954).

Immediately after occlusion of a main coronary ramus, the communicating arteries would probably be sufficient to transmit only 2 to 5 per cent of the normal inflow of the occluded artery (Wiggers and Green, 1936). After progressive gradual occlusion, however, these communicating channels enlarge until they are capable of supplying 50 to 100 per cent of the normal inflow (Gregg *et al.*, 1939; Fishman and Courmand, 1953). Exercise increases the extent of development of collateral communications (Eckstein, 1957).

Communications are seen between the myocardial vessels and the ventricular cavities (arteriololuminal vessels). While they may serve as accessory paths for venous drainage, it is unlikely that they can serve as sources of arterial blood for the nourishment of the myocardium (Gregg, 1946).

Electrical Activity of Heart. For a discussion of the electrical activity of the heart, see standard reference books on electrocardiography.

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Physiology of the Heart

B. Abnormal Cardiac Function*

HAROLD D. GREEN

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I. CARDIAC IRREGULARITIES

Disturbances in Initiation of Impulse

RHYTHMS ARISING IN SINOATRIAL NODE

Sinus Tachycardia. Sinus tachycardia represents a regular sinus rhythm at a rate above 100 beats per minute (Table V-1, a).

Sinus Bradycardia. Sinus bradycardia is a regular sinus rhythm at a rate of 45 to 60 beats per minute (Table V-1, b). During ex-

* Editor's note. Owing to limitation of space, this section has been condensed. For fuller discussion of subjects covered and for older references, see first edition.

cessive cooling of the body, the slowing appears to be a direct effect of cooling of the heart muscle (Cookson and DiPalma, 1955).

Sinus Arrhythmia. Sinus arrhythmia represents a variation in the heart rate which is usually associated with respiration; the rate increases during inspiration and decreases during expiration (phasic sinus arrhythmia). The arrhythmia is more marked in the young than in the aged. It is believed to be the result of impingement upon the cardio-regulatory center of afferent impulses from the

lungs carried by the vagi (Hering-Breuer fibers). Variations in the heart rate may also accompany Cheyne-Stokes respiration. Sinus arrhythmia is abolished by factors which decrease vagal tone (Table V-1, c).

PASSIVE RHYTHMS OF ECTOPIC ORIGIN

Rhythms of passive ectopic origin have a rate of 80 or less per minute. They are usually caused by failure of the sinoatrial node to maintain a normal rate of initiation of impulses, with the result that a lower center takes over the function of initiating the impulses.

Atrioventricular Nodal Rhythm. Atrioventricular nodal rhythm is regular but the rate is usually slower (30 to 50 beats per minute) than sinus rhythm. This rhythm may be seen after administration of too much digitalis and in atherosclerotic heart disease (Table V-1, b).

Wandering Pacemaker. Under certain conditions the pacemaker function may wander back and forth between the sinoatrial node and the atrioventricular node, probably because of rhythmic depression and enhancement of activity in the sinoatrial node. Indicative of such a shift is the characteristic slowing of the heart rate with electrocardiographic inversion of the P waves and shortening of the P-Q intervals, usually to less than 0.10 second, whenever the atrioventricular node becomes the pacemaker. Such shifting may be the result of varying intensity of the vagal nerve impulses impinging on the sinoatrial node.

Idioventricular Rhythm. An idioventricular rhythm is usually seen only during complete heart block. The ventricular rate is commonly about 30 beats per minute. The impulse usually originates below the atrioventricular node (as evidenced by the lack of retrograde conduction to the atrium) but above the branching of the Purkinje system, since normal QRS-T complexes are recorded (Table V-1, b). Idioventricular rhythm may also originate below the branching of the Purkinje system, or the impulse may originate above the bifurcation in a person with pre-existing bundle-branch block; in either case, the QRS com-

plexes are abnormal and resemble those of premature ventricular beats. It is postulated that aberrant QRS-T contours occurring during escape-beats could result from impulses originating in proximal portions of the A-V node and transmitted to the ventricle by normal as well as by preferential nodal pathways (Pick, 1956).

ACTIVE ECTOPIC RHYTHMS

An active rhythm develops when, following a normal beat, some part of the heart gives rise to impulses that have an interval which is shorter than the normal interval between two sinoatrial impulses. If this occurs only occasionally and for brief intervals, premature beats result; with prolonged enhancement of initiation of ectopic impulses, paroxysmal tachycardias are produced.

Premature Atrial Beats. A premature atrial beat usually spreads to and activates the sinoatrial node. As a result, the interval from the preceding normal beat to the premature beat is shortened. The interval from the beginning of the premature beat to the next normal beat is usually slightly longer than one normal interval, but the interval from the beginning of the preceding normal beat to the beginning of the following normal beat is less than two normal beats. In other words, the pause following the premature beat is not fully compensatory (Table V-1, c).

Premature Ventricular Beats. Premature ventricular beats usually arise below the branching of the special conduction system. The premature ventricular beat is usually not transmitted back through the atrioventricular node and does not discharge the sinoatrial node. While the interval from the beginning of the preceding normal beat to the beginning of the premature beat is shorter than normal, this decreased interval is compensated by an increase in interval from the beginning of the premature beat to the beginning of the next normal beat; so that the sum of the two intervals is equal to the sum of the intervals of two normal beats (Table V-1, c). The velocity of transmission of the premature beat through the ventricular wall is about 0.3 meters per second. The direction of fiber has

no clear influence on the spread of the excitation (Scher and Young, 1955).

In pulse tracings, a premature beat (particularly if of ventricular origin) is associated with a weak pulse or sometimes with absence of pulse in the arteries, owing to a small systolic discharge when the chamber (particularly the ventricle) contracts before it has had time to fill adequately. The first beat following the premature beat is always larger than normal.

Ventricular premature beats are most often associated with aortic insufficiency, or atherosclerotic or hypertensive heart disease. Atrial premature beats are most often encountered in mitral stenosis, and frequently in acute infections such as diphtheria and scarlet fever. Organic heart disease is almost always present when premature beats arise from multiple foci. Premature beats are rarely seen with heart rates over 120 per minute.

Pulsus Bigeminus. Pulsus bigeminus represents a regularly recurring premature beat, usually arising in the ventricle. Such beats are seen frequently after overdoses of digitalis.

Interpolated Extrasystoles. Interpolated extrasystoles are seen only with slow ventricular rates. Such interpolated extrasystoles arise in the ventricle and occur sufficiently early in the diastole of the preceding normal beat to give the ventricle time for full recovery before the next normal sinoatrial beat arrives.

Paroxysmal Tachycardias. Like premature beats, paroxysmal tachycardias may arise in the atrium or the nodal (supraventricular) tissue or the ventricle. In essence, they represent a series of regularly occurring premature beats and the complexes are similar to those described above, under Premature Beats (Table V-1, a). A series of rapid premature atrial beats may result from a single electrical shock applied to the atrium in the "vulnerable period" during the relatively refractory period of the atrial cycle (Orias *et al.*, 1950). With increased intensity of the shock, atrial fibrillation may result.

Ventricular tachycardias have essentially the same rates as atrial tachycardias and are often associated with organic heart disease, especially

coronary disease. During either atrial or ventricular paroxysmal tachycardia, the murmurs of mitral stenosis are frequently absent. Even in otherwise normal hearts, the electrocardiograms, during and for several days after an attack of paroxysmal tachycardia, may show widened and inverted T waves and prolonged Q-T intervals in the limb-leads.

Atrial Flutter. Atrial flutter represents a rapid regular rhythm originating at an abnormal site in the atrium (Table V-1, a). Some studies suggest that the rhythm may result from rapid initiation of impulses from a unitary focus (Scherf *et al.*, 1948; Prinzmetal *et al.*, 1950). However, DiPalma and Schultz (1950) have reviewed in great detail the literature dealing with ectopic cardiac arrhythmias, and particularly that concerned with flutter and fibrillation, and have arrived at the opposite conclusion. They believe that all such arrhythmias originate, not because some area of the heart is hyperirritable, but rather because of the presence of one or more depressed areas having prolonged relatively refractory periods and even more prolonged conduction rates. These areas of partial block, which may be very small, allow re-entry of the impulse previously generated by some other region or previously passed by the blocked area, and thus appear to become rapidly discharging foci.

Atrial Fibrillation. Atrial fibrillation is an irregularity in initiation of atrial impulses in which the atrial rate may be between 300 and 500 per minute (Table V-1, c). Cardiac catheterization demonstrates that these arrhythmias significantly impair cardiac function, especially in association with intrinsic heart disease. Reversion to a normal rhythm increases cardiac output and lowers right atrial pressure and pulmonary blood volume (Hansen *et al.*, 1952; Harvey *et al.*, 1955).

The following theories have been advanced to account for initiation of the rapid impulse: (1) a rapid circus wave of irregular path is present (DiPalma and Schultz, 1950); (2) several centers of rapid formation of stimuli are active (Prinzmetal *et al.*, 1950). Prinzmetal and co-workers (1955) claim that high-speed motion-pictures of the exposed human heart demonstrate

a chaotic disturbance consisting of heterorhythmic large and small waves, occurring simultaneously at rapid and irregular rates, no circus movement was found. They believe that (a) the irregularity starts as flutter, induced by rapid discharge from a single ectopic focus with orderly spread, (b) as the frequency of initiation of the impulse increases, there is a breakdown of orderly activity, since the atrium no longer can respond in a coordinate manner; and that (c) quinidine and other antifibrillatory drugs convert the fibrillation to flutter and finally to normal rhythm by suppressing the activity of the ectopic focus rather than by "closing the gap" in a circus wave.

In experimental animals, atrial fibrillation can be induced by intravenous injection of acetylcholine, together with administration of anticholinesterase (Loomis and Krop, 1955) or thyroid extract (Leveque, 1956), and by a single electrical shock applied to the atrium in the "vulnerable period" during the relatively refractory phase of the atrial cycle (Orias *et al.*, 1950). Atrial fibrillation usually starts as a short series of accelerating premature beats (DiPalma and Schultz, 1950). Once fibrillation starts, it usually persists throughout life unless stopped by administration of quinidine.

The coronary blood flow tends to be reduced during atrial fibrillation, but the reduction is less than the corresponding decreases in cardiac output and aortic pressure. It is believed, therefore, that either the systolic extravascular compression of the coronary vessels or the coronary vasomotor tone is reduced (Wegria *et al.*, 1950a, b).

Ventricular Fibrillation. Ventricular fibrillation in man is almost invariably fatal. It probably represents the occurrence of a circus movement of excitation of the ventricles. Ventricular fibrillation in man is usually a terminal event unless the process is stopped by "countershock," as noted below (Table V-1, c). However, instances of transient recurrent attacks of ventricular fibrillation have been reported in patients without organic heart disease (Robertson and Mathews, 1952; Dupler, 1953). These patients experienced syncope during the attacks.

Ventricular fibrillation is initiated most commonly by coronary occlusion but also may be induced during surgery of the heart by accidental mechanical or electrical excitation of the ventri-

cle during early diastole, *i.e.*, during the "vulnerable" or relative "refractory period" (Wiggers, 1940). The "vulnerable period" probably coincides with the period of increased excitability which Suckling and co-workers (1950) noted in animals about 160 milliseconds after the onset of a previous excitation, the threshold for excitation appears to rise with intervals of 180 milliseconds, and then falls to its lowest level with intervals of 230 or more milliseconds. DiPalma and Schultz (1950) believe that an area of partial block, caused by myocardial depression, is essential for the genesis of fibrillation, and that the basic mechanism is essentially similar to that in ectopic beats and flutter. Ventricular fibrillation can also be induced by local cooling of a portion of a ventricle (Scherf *et al.*, 1955) and by injections of epinephrine during chloroform anesthesia (Dyer and Ferguson, 1954).

If the heart can be exposed and subjected directly for a brief period to alternating current of the value of about 1.5 to 2.1 amperes, fibrillation can be stopped (Leeds *et al.*, 1951; Dyer and Ferguson, 1954, Zoll *et al.*, 1956), probably because simultaneous excitation of all parts of the ventricle by the strong current makes the entire ventricle refractory and thus prevents the spread of the circus movement of excitation. The ability to stop fibrillation and restore the normal rhythm has made possible open cardiac surgery in "quiescent" (fibrillating) hearts. Metabolic studies indicate that the oxidative requirements may be lower during fibrillation than in a normally working heart (Paul *et al.*, 1954) but greater than in a non-working heart (Jardetzky *et al.*, 1956).

Disturbances in Conduction of Impulse

Sinoatrial Block. Sinoatrial block is believed to occur when beats are suddenly dropped without other interruption in the rhythm; in other words, when the interval between two beats suddenly becomes twice the normal length (Table V-1, d). This rather rare condition is believed to be caused either by inability of the atrium to respond to the impulse from the sinus or by some form of block existing temporarily between the sinoatrial node and the atrial tissue.

Intra-atrial Block. Intra-atrial block has been described from electrocardiographic

tracings only; it is characterized by the presence of broad, notched or prolonged P waves (Walters and Grishman, 1954).

Wolff-Parkinson-White Syndrome ("Fusion Beats"). This syndrome can be diagnosed only from the electrocardiogram. It is characterized by a short P-Q interval and a prolonged QRS, and is thought to represent a precocious excitation (and contraction) of a limited portion of the left, or sometimes of the right, ventricle. The early excitation is thought to be induced by an accessory pathway from atrium to ventricle, in which conduction is less delayed than through the atrioventricular node (Bandiera and Antognetti, 1958). (See Table V-1, *d*.)

Delayed Conduction (First Degree Block, Incomplete Block). Delayed conduction represents a slowing in the rate of propagation of the cardiac impulse from the atrium through the atrioventricular node and Purkinje system to the ventricle. It is caused by damage to, or depression of, the atrioventricular node and the conduction tissue (Table V-1, *d*).

Prolonged Refractory Period (Dropped Beat, Second Degree Block, Partial Block). If for any reason the atrioventricular node and conduction tissue recover less rapidly than normally from a previous beat, *i.e.*, if the refractory period is prolonged, then the second impulse from the sinoatrial node may arrive at the atrioventricular node before it is fully recovered from the first. Under these conditions, the second beat fails to get through and the ventricle does not respond until the third sinus beat, giving a two-to-one heart block. In these conditions, there may be a combination of prolonged conduction and prolonged refractory periods (Table V-1, *b*).

Interference and Dissociation. Interference refers to failure of the second of two closely spaced impulses from the same or different sources to activate a portion of the heart, owing to the normally long refractory state of heart tissue which follows its excitation by the first impulse. Dissociation denotes that the heart is activated first by one, then by another pacemaker. In both instances, the re-

fractory periods are assumed to be within normal limits, in contrast to block in which the refractory period is usually prolonged. The phenomena of interference and dissociation may lead to a number of complex arrhythmias. The sinus beats may occasionally fall in the nonrefractory period of the atrioventricular node and produce a beat of the ventricle. These forms of arrhythmia resemble those seen with atrioventricular block (Burchell, 1949).

Synchronization (Accrochage). Occasionally patients with complete A-V block may show short periods of apparent or actual synchronization between atrial and ventricular beats (Marriott, 1956).

Concealed Atrioventricular Conduction. Frequently a premature beat may be transmitted through the atrioventricular node (either forward or backward) and then be blocked before it excites the next chamber. The effect of the concealed conduction may be noted, however, by the prolongation of the next P-Q interval or failure of the next impulse from the pacemaker to be transmitted (Langendorf and Pick, 1956).

Complete Heart Block. Complete heart block is characterized by a very slow ventricular rate which is independent of the atrial rate. It usually develops suddenly and may persist permanently (Table V-1, *b*). Temporary periods of heart block have been noted during reflex vagal stimulation induced by massage of the carotid sinus (Schwartz and Eichna, 1950).

The P-P interval of the atria may occasionally vary with the time of occurrence of the ventricular beat. This is caused in part by cyclic changes in vagal tone with each ventricular beat (Rosenbaum and Lepeschkin, 1955).

"Fusion" Beats. A beat of the atria or ventricles may be caused by two impulses arriving at the chambers so close together that only one beat results. Malinow and Langendorf (1948) have given a detailed classification of such fused beats and indicate that they may arise (a) from two sources, *e.g.*, in the atria, from the sinoatrial and atrioventricular nodes or, in the ventricles, from the atrioven-

tricular node and from an idioventricular beat; or (b) from one source, such as that seen in the syndrome of the short P-Q interval and prolonged QRS complex. For further discussion of this syndrome, see pages 168 and 204.

Bundle-Branch Block. Intraventricular Block. In bundle-branch block the impulse is delayed in its spread through some part of the ventricles. This may result from injury to a portion of the specialized conduction tissue so that the impulse must be conducted by ordinary myocardial tissue past the area of block, following which it re-excites the more distal conduction tissue, allowing excitation of the remainder of the heart. The impulse is delayed during its spread through the ordinary myocardium so that the time required for excitation of both ventricles is longer than normal. The terms "intraventricular block" (Rosenman *et al.*, 1950) or "left- (or right-) sided retardation" (Rasmussen and Moe, 1948) have been suggested as preferable to "bundle-branch block" in designating the condition of delayed conduction in a portion of the ventricle. The latter authors found evidence of damage to the bundle in only 14 of 72 cases. In intermittent bundle-branch block, the block appears with increase and disappears with slowing of the ventricular rate (Shearn and Ryland, 1953).

It has been generally thought that bundle-branch block indicated a grave prognosis. However, in a survey of 100 cases of such block, 28 were found in patients under 40 years of age and 7 in patients under 20 years of age, 29 had no other evidence of organic heart disease, and it was known that many of the patients had bundle-branch block for at least 10 years. It was, therefore, concluded that patients with bundle-branch block have a much more favorable prognosis than had been previously believed (Langley *et al.*, 1947).

Pulsus Alternans. Pulsus alternans represents alternating strong and weak beats of the ventricles with a regular rhythm. The alternations are usually noted on palpation of the pulse, registration of the arterial pressure pulses or arterial pressures; but alternation may also be seen in the amplitude of the QRS

and ST complexes in the electrocardiogram (Groedel and Miller, 1949). Ventricular alternation is seen most commonly with coronary artery disease and, as such, has a moderately serious prognosis. The alternation can occur independently in either ventricle, is usually but not always associated with hypertension in the corresponding arterial system (Ferrer *et al.*, 1956), and may be accentuated by factors which tend to decrease venous return.

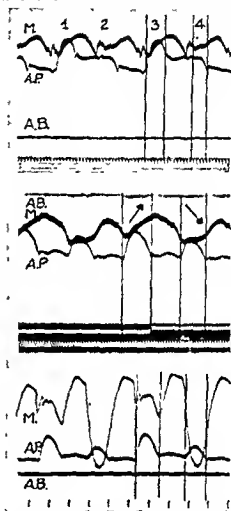


Figure V-12. Three examples of pulsus alternans. AP, aortic pressure; AB, base line for aortic pressure; M, myographic record. Downward movement of the myographic record indicates lengthening, upward movement indicates shortening of the myocardial fibers. In these studies the area of muscle, to which the myograph was attached, was rendered partially ischemic. Note the alternate large and small pulsations in the aortic pressure curve. The strong pulsations coincide with shortening, the weak pulsations with extension of the muscle fibers. The rhythm is regular. (Reproduced from Green, 1936).

Pulsus alternans is probably the result of prolongation of the refractory period of part of the myocardial fibers which are rendered partially ischemic by the arterial disease (Figure V-12).

General Comments. *Age.* Irregularities occurring before the tenth year usually represent sinus arrhythmias, although heart block and premature contraction may be seen, particularly accompanying enlargement of the heart. Atrial fibrillation rarely occurs before the age of 17. *Frequency.* The most common irregularity is atrial fibrillation which accounts for approximately 40 per cent of disturbances. Next most frequent are premature ventricular contractions which account for about 35 per cent of irregularities, and alternation for 10 per cent. Paroxysmal tachycardia, heart block and flutter together make up the remaining 15 per cent of arrhythmias. At

least 5 per cent of the irregularities are associated with cardiac failure. *Heart rate.* Heart rates of 35 and below usually indicate complete heart block. Rates of 40 to 50 suggest prolonged refractory period. Persistent rates of 130 and over, associated with a regular rhythm, indicate tachycardia and rates of 120 and over, with an irregular rhythm, usually represent atrial fibrillation. Atrial fibrillation is the most persistent. Other irregularities are usually transient.

Stokes-Adams Seizures. Syncopal attacks or convulsive seizures, resulting from inadequate cerebral blood flow for periods varying from 3 to 9 seconds, may be induced by (a) a prebrillatory type of ventricular tachycardia or flutter, (b) ventricular fibrillation, (c) complete cardiac standstill, or (d) ventricular asystole with maintenance of atrial beating (Bellet, 1957).

TABLE V-1

Differential Diagnosis of Cardiac Irregularities, Based on Principal Clinical Signs

a. *Tachycardias*

<i>Designation</i>	<i>Rate, Rhythm</i>	<i>Affected By</i>	<i>Course, Symptoms</i>	<i>Causes</i>	<i>Electrocardiogram</i>
Sinus	120-170, regular		Gradual onset and disappearance. Duration, minutes to days	Exertion, anoxia, emotion, atropine, amyl nitrite, thyroxin, hyperthermia, heart failure, shock and hemorrhage	P-Q low normal, QRS normal, Q-T shortened
Paroxysmal atrial. (Two to six times as frequent as ventricular)	120-200, usually 160-180; up to 300 in infants; regular	May occasionally be stopped with exercise, carotid pressure, deep breathing and Mecholyl, does not vary with exercise. Rate may remain slow after release of pressure. May stop with quinidine	Sudden onset and disappearance. Duration, seconds to hours. May be unnoticed or associated with dyspnea. May induce angina, fainting or mild heart failure	Unknown cause or exertion, fatigue, indigestion, infection, heart disease, use of tobacco, alcohol or digitalis	Rapid regular premature atrial beats, i.e., inverted or diphasic waves; normal QRS or widened inverted T waves. Occasionally 2:1 block or bundle-branch block with very rapid rate
Ventricular. (Rare, serious, active)	As in paroxysmal atrial. May be slightly irregular	Digitalis contra-indicated; may precipitate fibrillation	As in paroxysmal atrial	Often associated with organic heart disease	QRS resembles a premature beat; atria may beat independently or may fibrillate, or there may be backward conduction
Nodal atrioventricular. (Very rare, active)	As in paroxysmal atrial but may be as slow as 90		As in paroxysmal atrial	As in paroxysmal atrial	Regular retrograde atrial response or absent P waves; QRS-T as for atrial tachycardia
Atrial flutter. (One-fourteenth as common as atrial fibrillation)	Atrial rate 200 to 400, average 300. Ventricular rate usually one-half atrial rate, rhythm usually regular	Not affected by exercise, rest. Pressure on carotid sinus may halve rate by causing 2:1 block or changing this to 4:1 block, with return to former rate on release of pressure. Digitalis may convert flutter to fibrillation. Quinidine may convert to normal sinus rhythm	May be paroxysmal, last hours or years. Symptoms depend on ventricular rate	Circus wave? More common in presence of heart disease. Three times as common in males. More frequent after age 40	Usually 2:1 A-V block. May also be intraventricular block or complete A-V block. Regular rhythm. F waves, rather than distinct P waves
Atrial fibrillation, see under <i>c.c. Other Arrhythmias</i>					

TABLE V-1, *continued*b *Bradycardias*

<i>Designation</i>	<i>Rate. Rhythm</i>	<i>Affected By</i>	<i>Course. Symptoms</i>	<i>Causes</i>	<i>Electrocardiogram</i>
Sinus bradycardia	45 to 60			Occurs in sleep and in athletes. Inhalation of irritant gas, pressure on eyeballs and carotid sinus, increased intracranial pressure, jaundice, epidemic parotitis, influenza, excess of digitalis	Lengthening of P-Q, Q-T and Q-waves
Partial heart block Dropped beats, second degree block	30 or more	Exercise or amyl nitrite may abolish	May appear suddenly. May be associated with fainting. Jugular pulse may reveal isolated atrial pulse waves. Atrial heart sound may be present. Sometimes Adams-Stokes syndrome	Digitalis, myocardial damage, severe infections (typhoid, diphtheria, influenza, scarlet fever, pneumonia), coronary artery disease	Ventricular rate may be faster with faster atrial rate (4:3, 3:2, 2:1 or 3:1 block may be present)
Atrioventricular nodal rhythm	30 to 50, average 40, but as high as 80, per minute, regular	May be returned to sinoatrial rhythm with atropine or exercise	Sometimes Adams-Stokes syndrome	Marked depression of sinoatrial node	P wave may be inverted, P-Q short, or P wave may follow QRS
Complete heart block, sinus standstill, idioventricular rhythm (passive)	Ventricular rate averages 30 per minute	Not affected by exercise	May appear suddenly. May be associated with fainting. Jugular pulse may have atrial waves. Atrial heart sounds may be heard. Sometimes Adams-Stokes syndrome	Myocardial damage, severe infections (influenza, typhoid fever, scarlet fever, diphtheria, pneumonia), coronary artery disease	Atrial rate about 70, ventricular rate about 30 per minute. Normal ventricular complexes

TABLE V-1, continued

c. Other Arrhythmias

<i>Designation</i>	<i>Rate, Rhythm</i>	<i>Affected By</i>	<i>Course, Symptoms</i>	<i>Causes</i>	<i>Electrocardiogram</i>
Sinus arrhythmia	Normal rhythmic speeding and slowing with respiration	Abolished by exercise, atropine, hemorrhage (i.e., on speeding of rate), contrary to atrial fibrillation	Normal	Normal	Normal
Premature atrial contractions	Normal		Usually none	Atrial myocardial anoxia, heart failure, rheumatic fever	P wave inverted or has other abnormal shape; shorter preceding P-P interval than normal
Premature ventricular contractions	Normal		Prolonged pause	Ventricular myocardial anoxia, coronary artery disease	Abnormal QRS, prolonged, high voltage
Pulsus bigeminus	Normal		Usually none	Digitalis poisoning, re-entry rhythm	Second beat similar to premature ventricular beat
Pulsus alternans	Normal, Rhythm regular		Alternate pulses are weaker than normal	Cardiac insufficiency plus prolonged refractory period of part of myocardial fibers	Rhythm regular. Alternate beats may have lower voltage
Atrial fibrillation	Atrial rate 300 to 500, average 400. Ventricular rhythm irregular, 130-150 per minute	May vary with excitement and emotion. Digitalis slows heart by increasing A-V block. Amyl nitrite, exercise and atropine abolish arrhythmias of sinus origin but not those of fibrillation. Quinidine frequently converts to normal sinus rhythm	Patient conscious of irregular heart action, palpitation. Rhythm grossly irregular. Pulse deficit. Absence of presystolic mitral murmur and absence of triple jugular venous pulse	Circus movement, commonly associated with heart disease, especially mitral valve disease. Two or three times as common in males	P waves absent, or fine P waves present. QRS normal but irregularly spaced
Ventricular fibrillation		May be abolished by immediate massage and "countershock"	Arterial pressure falls to zero, respiration stops. Most common cause of sudden death	Coronary occlusion. Electric shock	Fine wavelike undulations. Absence of QRS-T complexes

TABLE V-1, continued
d. *Abnormalities Diagnosed Only by Electrocardiogram*

Designation	Rate, Rhythm	Affected By	Course, Symptoms	Causes	Electrocardiogram
Prolonged conduction, First degree block, incomplete block	Normal	May be shortened by atropine		Digitalis, rheumatic fever, damage to A-V node and conduction tissue	P-R interval 0.21 to 0.50 second
Interpolated extrasystoles	Normal			Likely to occur only with relatively slow atrial rate	Ventricular premature beat placed so that refractory period is over before next atrial beat
Bundle-branch, intraventricular block	Normal		Usually permanent	Damage to one bundle branch	All ventricular beats resemble premature beats in appearance, i.e., higher voltage and prolonged duration
Wolff-Parkinson-White syndrome (fusion beats)	Normal		(Paroxysmal tachycardia may be mistaken for this syndrome)	Congenital origin, bundle of Kent	Short P-Q with prolonged QRS
Sinoatrial block	Normal except for missing beats		No symptoms	Vagotonic state, atherosclerotic heart disease, digitalis poisoning	Occasional absence of P and QRS-T
Intra-atrial block	Normal			Coronary artery disease?	P waves broad, notched or prolonged

2. STRUCTURAL DEFORMITIES OF HEART

Acquired Valvular Defects

Mechanisms for Production of Murmurs. It is generally believed that eddy currents are responsible for the production of cardiac murmurs and Korotkow sounds. In a tube of a given size, eddy currents develop whenever the velocity of flow exceeds, or the viscosity drops below, a critical figure. Increase in the diameter of a vessel, for a given viscosity and mean velocity, increases the likelihood of eddy currents. Eddy currents develop at lower velocities of flow whenever the tube is suddenly dilated or becomes bent or angulated. The cardiovascular system is so constructed that it normally operates just below the critical level for the production of eddy currents (Green, 1950).

Rodbard and Saiki (1953) believe the murmurs are a result of alternate starting and stopping of the stream. The stream stops because of col-

lapse of the vessel or valve opening at its point of narrowing, owing to lowering of lateral pressure associated with a high velocity of flow; and the flow starts because the energy of motion is converted into pressure which forces open the collapsed segment. The frequency of the sound will be highest (300 repetitions per second) with strong degrees of narrowing or compression; the frequency falls as the degree of compression of the orifice is lessened, and at a critical diameter the flow becomes constant and the sounds disappear.

Grading of Murmurs. For convenience in following changes in cardiac lesions and in interpreting their significance, many clinicians grade the loudness of murmurs. Levine (1933) has graded a murmur 1+ if it can just be heard after careful auscultation, and 6+ as the loudest possible murmur which can usually be heard with the unaided ear at some distance from the chest. Murmurs be-

tween these extremes are graded 2+ to 5+. On the basis of a follow-up of rejectees from World War II, White and associates (1949) reported that "slight (grade 2) systolic murmurs at the apex are borderline and open to careful scrutiny, as is also true of systolic murmurs of moderate intensity (grade 3) at the pulmonary valve area, especially when the pulmonary second sound is unduly accentuated." Aortic systolic murmurs were regarded as abnormal when more than very slight (grade 1) in intensity, and diastolic murmurs anywhere were adjudged abnormal.

Classification of Murmurs. Murmurs may be physiologic or pathologic. According to Levine and Harvey (1949), nonsignificant functional (physiologic) systolic murmurs are often heard in anemia, owing to the accompanying increased cardiac output and resulting higher velocity of flow and the concomitant reduction in viscosity of the blood. Murmurs may also be heard during fever, hyperthyroidism and exercise, tachycardia may occasionally bring out systolic murmurs and at other times suppress them. It is probable that the murmurs are caused primarily by the increased velocity of blood flow associated with these conditions. They believe that, in the absence of fever, tachycardia, hyperthyroidism and anemia, a grade-2 apical systolic murmur is more likely produced by an organic mitral insufficiency than by physiologic causes.

Murmurs may also be classified as those caused by ejection or by regurgitation. (1) *Ejection-murmurs* are separated from the first sound by isometric contraction, are crescendo-decrescendo (diamond-shaped) and end appreciably before the second sound. They are caused by ejection of blood from the left or right ventricle in the presence of (a) stenosis of a valve or tract, (b) increased forward flow, or (c) dilatation of the ascending aorta or pulmonary trunk. (2) *Regurgitant murmurs* are parasystolic, i.e., they begin with the first and end with the second sound, the volume of the sound is relatively constant; and such murmurs are associated with mitral or tricuspid regurgitation or with a left-to-right shunt in ventricular septal defect or patent ductus arteriosus (Leatham, 1958).

Aortic Valvular Disease. Aortic insufficiency. If the aortic valve fails to close properly, blood regurgitates into the ventricle during ventricular diastole. The volume of blood regurgitating may be as much as 50 per cent of the systolic discharge, in which case the stroke volume must be twice normal in order to maintain a normal rate of circulation through the body. The regurgitant fluid, added to the volume of blood entering the ventricle from the atrium, causes greater initial ventricular volume and tension and, thereby, a stronger ventricular systole, a larger systolic discharge, and a more abrupt rise in aortic pressure. The sharply-rising wave-front is transmitted to the periphery as a water-hammer pulse, giving rise to a tap felt by the palpating hand and to the pistol-shot pulse heard at the inguinal canal. The pressure in the ventricle and aorta begins to drop rapidly during the latter part of ventricular systole. As a result of this and of regurgitation of blood into the ventricle, the diastolic pressure falls below normal. The wide oscillation in pressure in the aorta causes sufficient fluctuation in the flow of blood into the capillaries to produce a rhythmic variation in color of the nailbed; this is designated the *capillary pulse*. Electrocardiographic studies of the aortic pulsations demonstrate a rapid diastolic decline in volume with diminution or absence of the normal post-incisural increase in volume. Records from the left ventricle show that systole is slightly prolonged, and that ventricular filling begins at the onset of protodiastole instead of at the end of isometric relaxation (Heyer *et al.*, 1950).

The stream of blood regurgitating through the aortic valve sets up high-pitched vibrations which are heard best, with the diaphragm-type of stethoscope, in the third left intercostal space. The sounds may be intensified by directing the patient to lean well forward and to hold his breath after full expiration. When the murmur is caused by a ruptured valve cusp, it may have a musical quality, called "dove-coo;" when this murmur is recorded, it appears to be virtually a pure sinuoidal wave (Groom and Boone, 1953).

Possibly because of partial closure of the mitral valve by the regurgitating aortic stream and possibly also because of eddy currents resulting from enlargement of the left ventricle, a murmur is produced which mimics that of mitral stenosis. This "false" murmur is called the Austin Flint murmur.

As a consequence of the increased initial ventricular volume and initial length of the myocardial fibers, the heart hypertrophies and compensates for the load. If the increase in this load is excessive, however, left ventricular function is depressed (Welch *et al.*, 1957) and heart failure may ensue. With excessive dilatation of the ventricle, the mitral ring may become dilated with resulting mitral insufficiency, this condition, together with excessive rise in ventricular diastolic pressure, may lead in turn to elevation of pulmonary arterial pressure and ultimately to right ventricular dilatation and failure.

The presence of a regurgitant stream may be detected and its magnitude estimated by injecting a suitable dye into the arterial stream at various levels of the aorta by means of a catheter passed up the aorta from the femoral artery. In normal persons the dye will be detected by a couvette attached to the right ear, only if the tip of the catheter is at the level of the aortic arch. The presence and the magnitude of the regurgitation can be estimated from the distance down the aorta at which an injection can still be detected by the ear couvette (Braunwald and Morrow, 1958).

Unusual features associated with aortic insufficiency include sudden death, excessive sweating, cervical (carotid artery) pain, abdominal pain, angina pectoris, pounding sensations and splashing sounds (Harvey *et al.*, 1957).

Aortic stenosis. Stenosis of the orifice of the aortic valve is frequently accompanied by aortic insufficiency. The opening must be reduced to from one-half to one-quarter of the normal to cause significant symptoms. The narrow opening increases the resistance to ejection by the ventricle. The blood thus retained within the ventricular cavity, combined with the normal inflow from the atrium, leads first to ventricular dilatation and then to a steeper rise of pressure during isometric contraction and to development of sufficient pressure to eject the normal quantity of blood through the narrowed opening. The passage of the blood through the narrowed opening

into the wider aorta gives rise to a thrill and to a loud systolic murmur which may be detected in the second right intercostal space and often extends into the neck. At times, however, the only physical sign may be a harsh systolic murmur at the apex (Bergeron *et al.*, 1954).

The entrance of blood into the aorta is less rapid than normal and the pulse has a correspondingly slow rise. The contour of the brachial pressure curve serves to confirm the presence of aortic stenosis, but is not diagnostic of this condition (Hancock and Abelmann, 1957).

Coronary circulation is impaired during systole with aortic stenosis, and during diastole with aortic insufficiency. Pulsus alternans and premature systoles may be observed in these conditions. The electrocardiographic changes recorded with aortic insufficiency and aortic stenosis are those associated with left ventricular hypertrophy. The uncalcified stenosed aortic valve is more suitable than the calcified valve for attempts at valvulotomy. If the valve is calcified, forcible dilatation does not result in much increase in the orifice and may produce valvular incompetence (McMillan, 1955). (See Chapter XVII, page 1032.)

Mitral Valvular Disease. *Mitral insufficiency.* Mitral insufficiency is almost always associated with some degree of stenosis. A functional or relative insufficiency may, however, result from dilatation of the mitral ring by left ventricular dilatation (Levine and Harvey, 1949). During ventricular systole, blood is regurgitated into the atrium. During ventricular diastole, this volume of regurgitated blood is added to the venous blood normally returned, thus increasing the ventricular diastolic size and tension. The greater volume of blood in the atrium likewise leads to atrial dilatation and hypertrophy of mild degree. Atrial pressure rises slightly but, if there is minimal associated mitral stenosis, the atrium is able to empty relatively readily and the average pressure in the atrium is, therefore, only slightly above normal and the pulmonary capillary pressure not appreciably elevated. The flow of blood from ventricle to atrium through the narrow orifice into the larger atrial space gives rise to a systolic murmur of medium pitch which is frequently transmitted well out into the axilla. Mitral insufficiency

may develop suddenly as a result of rupture of a papillary muscle which is involved by infarction. When this occurs, a harsh systolic murmur is heard, and there is often associated pain and profound shock (Smith, 1950).

In experimental animals, mitral regurgitation with up to three times the resting cardiac output was tolerated with only slight alterations in effective cardiac output, or left atrial or ventricular pressure (Braunwald *et al.*, 1957). In patients, however, Draper and associates (1951) found, as with mitral stenosis (see below), that cardiac output may not increase adequately with exercise, the arteriovenous difference in oxygen concentration was increased at rest and greatly increased with exercise. These effects were even more marked with mitral insufficiency than with mitral stenosis. However, the right ventricle was not significantly enlarged unless there was actual heart failure.

Because of the importance of the presence of mitral regurgitation as a contraindication to mitral commissurotomy, various procedures have been devised for its detection and measurement. Gorlin and Dexter (1952) have attempted to calculate the effective cross-sectional area of the insufficient mitral valve from simultaneous measurements of pulmonary capillary and brachial arterial pressures and cardiac output. Gilman and associates (1958) have injected radiopaque material into the left ventricle during roentgenography. Absence of left atrial opacification is regarded as good evidence for competence of the mitral valve, and vice versa. By means of contrast angiography, after direct injection of the opaque media into the left atria, it was observed that the atria were largest when mitral insufficiency was associated with atrial fibrillation and next largest in the presence of atrial fibrillation alone. There was a rough negative correlation between the size of the atrium and that of the orifice in mitral stenosis (Lukas *et al.*, 1958).

Mitral Stenosis. The narrow opening interferes with the entrance of blood from the atrium into the ventricle and gives rise to a low-pitched rumbling murmur. This murmur is heard during the period of rapid ventricular filling in mid-diastole and is accentuated in late diastole during atrial systole, when a second rush of blood from atrium to ventricle occurs. The murmur is heard best in the apical region with the patient lying on his left side

and is accentuated by exercise or other factors which increase the cardiac output. In a group of patients who were surgically examined, 30 per cent of those found to have pure mitral stenosis had a mitral systolic murmur in addition to a diastolic murmur (Janton *et al.*, 1954).

The first sound is accentuated in the presence of mitral stenosis, giving rise to a snapping sound; this change in character may be noted even in the absence of audible murmurs (Levine and Harvey, 1949, Nichols *et al.*, 1955). The first sound may occasionally have a crescendo character resembling the presystolic murmur of mitral stenosis, yet phonocardiograms may show that the sounds all begin after the Q wave of the electrocardiogram (Alimurung *et al.*, 1949). Occasionally a third sound, called by some writers the "opening snap," may be heard at the apex in patients with mitral stenosis, even in the absence of murmurs.

Because of the resistance to emptying, the atrium becomes distended and hypertrophied, and atrial pressure tends to remain elevated. This gives rise in turn to an elevation of pulmonary capillary and pulmonary arterial pressure and frequently to right ventricular dilatation and hypertrophy. The cardiac output tends to be below normal at rest and fails to rise normally with exercise. The arteriovenous difference in oxygen concentration is elevated at rest and increases abnormally with exercise (Draper *et al.*, 1951; Gorlin *et al.*, 1951).

The roentgenogram shows an increase in the shadow of the right ventricular infundibulum and pulmonary trunk, and well-marked enlargement of the left atrial shadow which in the oblique position fills the clear space normally seen along the esophageal shadow. The right ventricle is usually not enlarged except in the presence of heart failure (Draper *et al.*, 1951). Gorlin and Gorlin (1951) have derived a formula by which they believe they can calculate the effective cross-sectional area of the normal or stenotic valve from measurements of pulmonary "capillary" pressure and cardiac output.

Correction of the stenosed mitral valve by various surgical procedures, (see Chapter XVII, page 1027) has become commonplace. Favorable operative results are usually associated with (a)

marked improvement in ability to increase the cardiac output, and a lesser increase in ventilation during exercise (Wade *et al.*, 1954); (b) greater capacity to perform moderate work (Landen and Bayer, 1954); (c) lowering of mean pressure in the pulmonary artery (Wood *et al.*, 1956), (d) cessation of formation of emboli, and (e) stabilization of, or decrease in, the size of the cardiac silhouette, whereas the hearts had been enlarging prior to surgery (Janton *et al.*, 1956). However, there is not as good correlation between the fall in pressure in the pulmonary trunk postoperatively and the severity of structural abnormalities in the lung (Coodale *et al.*, 1955).

Measurement of the pressures in the left atrium and left ventricle during operation indicate an insignificantly small gradient in ventricular filling pressure in the presence of a normal mitral valve. This pressure gradient becomes elevated in proportion to the degree of stenosis (Moscovitz *et al.*, 1955).

Of the first 50 patients in one series who underwent mitral commissurotomy, 41 were still living 4½ to 7 years following the operation. Four of the living patients no longer had any murmurs, 11 had lost their original mitral diastolic murmurs, and 14 had a mitral systolic murmur which was not present preoperatively. The authors thought that 71 per cent of the living patients and 88 per cent of those in the series were improved. The greatest improvement was obtained in patients with "pure" mitral stenosis (Janton *et al.*, 1956).

Patients in group IV (Criteria Committee, 1953, see also page 242 with evidence of left heart enlargement prior to operation, have the highest mortality rate and the least evidence of benefit (Julian *et al.*, 1954). Patients with pliable valves have the smallest number of failures (6.6 per cent), whereas 43.3 per cent of those with scarred, immobile, often calcified valves either die subsequent to the operation or are not greatly improved (Ellis *et al.*, 1954; Janton *et al.*, 1956). The rheumatic fever may be reactivated postoperatively in up to 24 per cent of patients whose lesion is on a rheumatic basis (Soloff *et al.*, 1953; Janton *et al.*, 1956). Approximately 30 per cent of patients with a previously normal rhythm develop atrial fibrillation postoperatively. In three-fourths of the patients the rhythm may revert to normal. No association is observed in the results of atrial biopsy and the onset of fibrillation; the latter is thought to result from atrial edema secondary to operative trauma (Dimond *et al.*, 1953). The presence of a significant degree of

mitral insufficiency is a contraindication to surgery of mitral stenosis. Evidence of left ventricular enlargement, and a loud (grade 4) systolic murmur, marked left atrial enlargement with systolic expansion, and symptoms of fatigability rather than dyspnea suggest that the mitral insufficiency is sufficiently advanced to render exploratory cardiomy inadvisable (Janton *et al.*, 1954). The contours of the pressure curves recorded from a catheter wedged in a small pulmonary artery (pulmonary "capillary" pressure) do not provide consistent evidence concerning the presence of mitral insufficiency (Coelho *et al.*, 1955; Overbeck *et al.*, 1955).

Atrial fibrillation frequently accompanies mitral stenosis, in which case the presystolic murmur (caused by atrial systole) is absent. The pulmonic second sound is frequently accentuated. The late complications in this condition are pulmonary congestion, right ventricular failure, and systemic arterial embolism from detachment of mural thrombi. Thrombi are more likely to form in the left atrium in the presence of mitral stenosis or atrial fibrillation, and are less likely to form in the presence of mitral insufficiency (Storck *et al.*, 1954).

Transbronchial registration of left atrial pressure is reported to be useful in evaluation of mitral valvular disease. The slope of the descent of the atrial pressure associated with rapid ventricular filling, divided by the amplitude of the atrial pressure just before the descent, was least in the presence of mitral stenosis and greatest in the presence of mitral insufficiency (Morrow *et al.*, 1957). Mitral disease (insufficiency or stenosis) has also been evaluated by means of curves showing concentration of radiopotassium, obtained by a catheter inserted into the femoral artery (Conn *et al.*, 1957).

The ventilatory response to exercise in the presence of mitral stenosis has been expressed in terms of the following formula:

$$\text{Oxygen removal ratio} = \frac{\text{ml. of oxygen extracted per min.}}{\text{L. of air breathed per min.}}$$

In normal persons, exercise (peddling with feet while lying prone) increased the ratio by 20 per cent from a control of 40.4 to 47.8. The response was similar in patients with mild degrees of mitral stenosis; but in the presence of severe stenosis, the ratio remained unchanged or fell with exercise. Since the changes could not be

correlated with cardiac output, it was concluded that they represented an altered ventilatory pattern (Ebnother *et al.*, 1957).

Pulmonary Valvular Disease. *Pulmonary insufficiency.* Pulmonary valvular insufficiency is almost always functional (resulting from dilatation of the pulmonary valve), being secondary to pulmonary arterial hypertension from any cause, although it may occur as a terminal event in subacute bacterial endocarditis. The regurgitation produces a blowing, early diastolic murmur heard along the left sternal margin, and leads to dilatation and hypertrophy of the right ventricle. Fluoroscopic examination reveals active pulsation of the pulmonary trunk and right ventricle.

Pulmonary stenosis. The stream of blood leaving the right ventricle sets up vigorous eddy currents as it passes through the stenotic orifice into the pulmonary trunk, giving rise to a harsh systolic murmur and a thrill in the second left intercostal space. A functional pulmonic systolic murmur is often heard in children and young persons; it is commonly heard when vascular resistance is low and cardiac output is high. Under such circumstances, the arterial pressure curve shows a steep ascent, a short plateau, and an incisura low on the descending limb (Spitzbarth, 1955).

The increased resistance to right ventricular ejection leads to incomplete emptying with resulting dilatation and hypertrophy of the right ventricle and, if severe, also of the right atrium. Fluoroscopic examination reveals the enlarged chambers and decreased pulsation of the pulmonary vessels. The patient usually suffers from stagnant anoxia owing to the slow rate of circulation of blood and this may lead to cyanosis. Dyspnea is common. Catheterization of the pulmonary trunk and right ventricle with registration of the pressure reveals a greater pressure in the ventricle than in the pulmonary trunk during systole (Courmand *et al.*, 1949, Dow *et al.*, 1950, Dimond and Lin, 1954). Right atrial pressure tracings reveal a giant *a* wave which represents a characteristic response of the right atrium in the presence of severe right ventricular hypertrophy (McCord *et al.*, 1953).

Criteria for the performance of pulmonary valvulotomy include: (a) clinical symptoms suggestive of right heart failure, such as episodes of syncope, systolic jugular pulse, and systolic pulsation of the liver, (b) decreasing saturation of systemic arterial oxygen; (c) electrocardiographic evidence of widening of QRS and increasing amplitude and width of the P waves, and (d) a minimum initial right ventricular pressure of 70 mm water.

Surgery seems adequate for valvular stenosis but is far from ideal for infundibular stenosis. (See Chapter XVII, page 1023.) Recordings of pressure before and after the attack on the valve are thought to be an important adjunct to the operative technique (Dimond and Lin, 1954); others report remarkably slight changes in right ventricular and pulmonary arterial pressures, in pulmonary flow and in pulmonary valvular area, measured at rest, despite uniform clinical improvement (Lurie and Shumacker, 1953, Fowler *et al.*, 1956). Direct approach to the pulmonic valve by way of the pulmonary trunk gives more physiologic improvement than does the approach through the wall of the right ventricle (Blount *et al.*, 1954).

Tricuspid Valvular Disease. *Tricuspid insufficiency.* Functional insufficiency may be seen with right ventricular dilatation in heart failure. Tricuspid insufficiency increases the work load on the right atrium and ventricle. The regurgitant stream gives rise to a systolic murmur heard best over the lower end of the sternum. This murmur is accompanied by an exaggerated, prolonged, positive systolic wave in the jugular pulse and in records of pressure obtained during right atrial catheterization, instead of the normal negative wave (Messer *et al.*, 1950); by a pulsation in the superior vena cava which can be seen during fluoroscopic examination; and by pulsation of the liver. All of these closely follow the first heart sound.

In acute experimental tricuspid insufficiency in dogs, atrial pressure is elevated only during the flow of the regurgitant stream in late systole and early diastole. In view of this occurrence, the increased average venous pressure in patients is apparently caused by some other factor, such as increased blood volume (Little, 1948).

Tricuspid stenosis. Tricuspid stenosis in-

duces low-pitched murmurs in mid-diastole and during atrial systole which are most readily heard over the lower end of the sternum. If tricuspid stenosis is present alone, no evidence of either left or right ventricular hypertrophy or of pulmonary hypertension will be found although the patient is markedly disabled; but the right atrium will be dilated and hypertrophied and the systemic venous and right atrial pressures will be elevated. Associated with the latter, there may be a strong atrial (*a* wave) pulsation in the jugular and atrial pulses, a presystole pulsation in the liver and a prominent P wave in the electrocardiogram (Yu *et al.*, 1956).

Bernheim's Syndrome. In this condition, the left ventricle is markedly dilated and hypertrophied and the ventricular septum bulges into the right ventricular cavity, interfering with the flow of blood into the right ventricle. This leads to marked hypertrophy and dilatation of the right atrium. Systemic engorgement occurs early; pulmonary congestion is noted only terminally (Russek and Zohman, 1950). Evans and White (1948), however, doubt that the above phenomena represents a true syndrome.

Congenital Defects

Congenital defects are discussed in detail in Chapter VI. Taussig (1947) has classified congenital defects into two groups: (a) those which deprive the body of an adequate amount of oxygenated blood and (b) those which permit the body to receive an oxygen supply sufficient for the growth of the individual. The former are usually associated with varying degrees of cyanosis.

Mechanisms Producing Cyanosis. *Average quantity of reduced hemoglobin in capillary blood necessary to cause cyanosis.* According to Lunds-gaard and Van Slyke (1923), visible cyanosis, *i.e.*, a purple or plum-colored discoloration of the skin, is seen whenever the cutaneous capillary blood contains an average of 5 grams of reduced hemoglobin per 100 ml. of blood. Assuming that 1 gram of hemoglobin transports 1.33 ml. of oxygen, the concentration of reduced hemoglobin can be expressed in terms of equivalent milliliters of reduced hemoglobin per 100 ml. of blood. Ac-

cordingly, cyanosis would be seen whenever this blood contains $5 \times 1.33 = 6.7$ equivalent volumes of reduced hemoglobin per 100 ml. of blood.

Normal average capillary concentration of reduced hemoglobin. In normal persons with 15 grams of hemoglobin per 100 ml. of blood, the concentration of fully saturated blood is 20 ml. of oxygen per 100 ml. of blood. The arterial blood will be 94 to 97 per cent saturated normally and will contain, therefore, about 19 ml. of oxygen per 100 ml. of blood. During its passage through the capillaries, the blood will give up approximately 5 ml. of oxygen per 100 ml. of blood and the venous blood will, therefore, have approximately 6 equivalent ml. of reduced hemoglobin ($1 + 5 = 6$ ml. per 100 ml. of blood), and 14 ml. of oxygen carried by the oxygenated hemoglobin. The average capillary concentration will be $\frac{1+6}{2} = 3.5$ equivalent ml. per 100 ml. blood, *i.e.*, well under the amount necessary to cause cyanosis.

Effect of quantity of blood in the capillaries on production of cyanosis. By constricting the efferent veins or dilating the cutaneous capillaries and venous plexus, it is possible to increase the quantity of blood in the skin, even though the rate of blood flow, the oxygen utilization, and the average concentration of reduced hemoglobin in the capillary blood be unchanged. Under these circumstances, if the quantity of blood in the skin is doubled, the amount of reduced hemoglobin per unit area of skin will be doubled and cyanosis will result.

Effect of increased cutaneous oxygen consumption on oxygen utilization and on average capillary concentration of reduced hemoglobin. Oxygen utilization means the amount of oxygen removed from each 100 ml. of blood flowing through the tissues. If the rate of uptake of oxygen by the tissues is augmented without a rise in the blood flow, there will be a proportional increase in the oxygen utilization and in the average amount of reduced hemoglobin in the cutaneous capillaries. If the oxygen utilization is augmented to 12 ml. per 100 ml. of blood flow, or to 2.4 times the normal, the average capillary blood will contain $\frac{1+13}{2} = 7$ equivalent ml. of reduced hemoglobin or enough to produce cyanosis that is just detectable.

Effect of cutaneous blood flow on oxygen utilization and average capillary concentration of reduced hemoglobin. With no change in either the rate of oxygen consumption by the tissues or the

quantity of blood in the cutaneous capillaries at any instant, a reduction in the rate of blood flow in the skin will also increase the oxygen utilization, i.e., the amount of oxygen removed per 100 ml. of blood flow. The cutaneous blood flow would have to be reduced to $\frac{5}{12} = 0.42$ of the normal rate in order to increase the oxygen utilization to the level of 12 ml. per 100 ml. necessary to cause cyanosis ($\frac{1+13}{2} = 7$).

Effect of admixture of venous blood with arterial blood in the aorta. If for any reason a mixture of arterial and venous blood enters the aorta, the concentration of reduced hemoglobin in the blood circulating in the arteries will be increased. If the concentration of hemoglobin, the rate of flow, and the oxygen consumption of the tissues are all unchanged, the quantity of reduced hemoglobin in the veins and the average concentration in the cutaneous capillaries will both be increased by such admixture of venous blood. The minimum amount of reduced hemoglobin which must be present in this mixture of blood when cyanosis is detectable can be computed as follows. Let X equal the level of reduced hemoglobin in the aortic blood necessary to cause such cyanosis. If we assume an oxygen utilization of 5 ml./100 ml., then cyanosis will be produced by an average capillary concentration of reduced hemoglobin of 7 equivalent ml.

per 100 ml. of blood: $\frac{X + (X+5)}{2} = 7$ and $X = 7 - 2.5 = 4.5$ equivalent ml. of reduced hemoglobin per 100 ml. in the arterial blood. The venous blood will then have $4.5 + 5 = 9.5$ equivalent ml. of reduced hemoglobin per 100 ml. The minimum amount of such venous blood that would have to be mixed with oxygenated blood containing 1 equivalent ml. of reduced hemoglobin per 100 ml. to produce cyanosis can then be calculated as follows:

Let Y equal the fraction of venous blood that is to pass directly from the right atrium or ventricle to the aorta. $1 - Y$ will equal the fraction that will flow through the lungs. Then

$$Y \times 9.5 + (1 - Y) \times 1 = 4.5$$

$$Y = 0.41$$

Thus, if 0.41 of this venous blood passes directly into the systemic arterial circuit and 0.59 goes through the lungs, cyanosis will be just detectable. The blood in the arteries would be $\frac{15.5}{20}$

$\times 100 = 78$ per cent saturated with oxygen.

Effect of polycythemia. Cyanosis frequently

accompanies polycythemia, especially when the oxygen capacity of the blood is more than 23.5 ml. per 100 ml. Increasing the level of hemoglobin in the blood usually results in the blood being less completely oxygenated during its passage through the lungs. If we assume that, as usual, only 19 ml. of oxygen are taken up by each 100 ml. of blood flowing through the lungs, the minimum concentration of hemoglobin that would be necessary to cause cyanosis would be 17.7 Gm. per 100 ml. of blood. This would give the blood an oxygen capacity of 23.5 ml. per 100 ml. and the arterial blood would contain reduced hemoglobin in the amount of $23.5 - 19 = 4.5$ equivalent ml./100 ml. As in the case of admixture of venous blood, this would give an average capillary concentration of reduced hemoglobin of $\frac{4.5 + 9.5}{2} = 7.0$ equivalent ml./100 ml., just

sufficient to cause cyanosis. Under such assumed conditions, the arterial blood would be $\frac{19}{23.5} \times 100 = 81$ per cent saturated with oxygen. In actual conditions, the arterial blood would probably take up more than 19 ml. of oxygen per 100 ml. of blood, but at the same time the blood volume and the quantity of blood in the cutaneous capillaries is increased in polycythemia, thus making the degree of arterial unsaturation more apparent.

Effect of anemia. Cyanosis is rarely seen in anemia and practically never when the oxygen capacity of the blood is less than 3 ml. per 100 ml. If the hemoglobin concentration were reduced just to 9.8 Gm./100 ml. of blood (oxygen capacity = 13 ml./100 ml.) and if the blood flow were slow enough so that all the oxygen was removed from the blood during its passage through the cutaneous capillaries, and if the arterial blood maintained the normal equivalent ml./100 ml. of reduced hemoglobin, then the average capillary level of reduced hemoglobin would be $\frac{1+13}{2}$

$= 7$ equivalent ml., i.e., just sufficient to cause cyanosis. Cyanosis would be unlikely at this degree and almost impossible with anemias of more severe degree, since in anemia it is unlikely that there would be as much as 1 equivalent ml. of reduced hemoglobin per 100 ml. of arterial blood and since the oxygen utilization would never be 100 per cent. Cyanosis also would be unlikely because the blood volume and the concentration of the blood in the cutaneous capillaries is less than normal in anemia.

Phenomena associated with cyanosis. When-

ever cyanosis is present for any length of time, clubbing of the fingers and toes is usually seen. Absence of clubbing usually means that the cyanosis is of recent origin. The clubbing represents an overproduction of capillaries, dilatation and thickening of the blood vessel walls, an increase in connective tissue and, when marked, thickening of the periosteum. The cause of its production is un-

certain since it may occur with some diseases of the gastrointestinal system in the absence of anoxia (Wiggers, 1949, p. 486). Clubbing is rarely seen in association with congenital heart disease, except when cyanosis is present. Cyanosis caused by congenital heart disease is usually associated with a shortened arm-to-tongue circulation time owing to the presence of a right-to-left shunt.

3. DISTURBANCES OF CORONARY CIRCULATION

Relative Insufficiency. Angino Pectoris

The term *relative coronary insufficiency* may be applied to any condition in which the coronary blood flow is not interrupted but is reduced below the immediate demands of any area of the myocardium. Such insufficiency is usually present for only a few seconds to minutes and ordinarily the associated disturbances are rapidly reversible upon relief of the state of insufficiency.

Hecht (1949) suggested the terms *myocardial ischemia without tissue destruction* for angina and *myocardial ischemia with tissue destruction* for coronary occlusion. However, tissue destruction can result from relative myocardial ischemia without occlusion, while coronary occlusion may not result in tissue destruction if there is adequate existing collateral circulation or if the patient dies soon after the onset of the attack (Wang *et al.*, 1948).

FACTORS LEADING TO CORONARY INSUFFICIENCY

Narrowing of Coronary Arteries. As described in Chapter VIII, the most common cause of narrowing of the coronary vessels is atherosclerosis. The reduction of flow varies with the degree of narrowing and with the length of the narrowed segment.

Resistance to flow. With a given arterial pressure, the rate of flow is dependent upon the sum of the resistances to flow in the arteries, arterioles, capillaries and veins, which, in electrical terminology, are arranged in series. Resistance can be expressed simply as the drop in pressure along the segment, divided by the rate of flow, *i.e.*, in mm. Hg/ml./min. A convenient unit for resistance is the peripheral resistance unit (PRU) = mm. Hg/l ml./min. (Green, 1950); it has the

same significance as the ohm in electrical terminology.

Effect of narrowing of a coronary artery when the coronary arterioles are constricted, i.e., when cardiac work is minimal. With the subject resting and the cardiac work at a basal level, the coronary arterioles are constricted and the resistance to flow through them is high.

For example, in the case of an artery which supplies blood to 100 Gm. of myocardium, the resistance to flow through the associated arterioles, capillaries and veins may be of the order of 99 mm. Hg = 1.24 PRU. The resistance to flow in the artery itself will be very low, of the order of 1 mm. Hg = 0.013 PRU, and the total resistance (aorta to coronary sinus) will be $0.013 + 1.24 = 1.253$ PRU. With an aortic pressure of 100 mm. Hg (coronary sinus pressure assumed to be zero), the normal flow would be $\frac{100}{1.253}$

= 80 ml./min. Flow = $\frac{\text{pressure}}{\text{resistance}}$; this is quite comparable to the equation used in electricity: amperes (rate of flow of current) = $\frac{\text{volts (electrical pressure)}}{\text{ohms (resistance)}}$.

If under resting conditions, the coronary artery were narrowed sufficiently to increase its resistance to flow 45-fold, *i.e.*, to 0.6 PRU, the total resistance would be elevated only to $0.6 + 1.24 = 1.84$ PRU. With the same aortic pressure used above, *i.e.*, 100 mm. Hg, the flow would be $\frac{100}{1.84} = 54$ ml./min. or 68 per cent of the normal. Resistance in a tube varies inversely as the fourth power of the radius. In order to increase the resistance 45-fold, the radius would have to be changed to: $\frac{\text{PRU}_1}{\text{PRU}_2} = \frac{R_1^4}{R_2^4}$; $\frac{1}{45} = \frac{X^4}{1^4}$; $X = 0.386$ where PRU = resistance, R = radius, and X = radius required to produce a 45-fold increase in

resistance if the original radius were assumed to be 1. Thus, a 45-fold increase in resistance can be produced by a decrease in radius to approximately one-third its previous value.

Effect of narrowing of a coronary artery when the coronary arterioles are dilated, i.e., when cardiac work is maximal. During exercise the cardiac work is increased and the coronary arterioles dilate. If, in the above example, the maximum dilatation of the arterioles is such that the resistance to flow through the arterioles, capillaries and veins is reduced 4-fold,* i.e., to 0.31, then, in the normal heart the total resistance would be $0.013 + 0.31 = \text{PRU}$. At an aortic pressure of 100 mm.

Hg, the coronary flow would be $\frac{100}{0.323} = 310$ ml./min. Narrowing the artery to the same extent as indicated above would cause the total resistance to be $0.06 + 0.31 = 0.91 \text{ PRU}$ and

the flow would be $\frac{100}{0.91} = 110$ ml./min. Thus

equals $\frac{110}{310} \times 100 = 35$ per cent of the expected flow, as compared to 68 per cent with the arterioles constricted. Thus, we see that narrowing of a large artery influences flow in inverse proportion to the degree of arteriolar constriction.

Compensatory arteriolar dilatation in response to narrowing of a coronary artery. We may look at the effect of constriction of a coronary artery in another way. Let us assume that in a subject at rest, the main coronary artery is narrowed sufficiently to reduce the flow to 68 per cent of normal (example 2 mentioned above). Compensatory dilatation of the arterioles will now occur, tending to restore the total resistance and, therefore, the flow towards normal. This dilatation, however, correspondingly diminishes the amount of dilatation which may occur during subsequent periods of increased cardiac work.

Aortic Pressure. Conditions such as aortic insufficiency, arteriovenous fistula, patent ductus arteriosus, communication of the sinus of Valsalva with the right ventricle, and excessive peripheral vasodilatation, all tend to produce marked lowering of the aortic pressure during diastole. Since most of the coronary flow occurs in diastole, this may lead to a serious reduction in diastolic coronary flow. The reduction in diastolic flow may be compensated by arteriolar dilatation which in-

creases to some extent the proportion of the total flow that occurs during systole. However, as noted in the paragraph above, this reduces the total amount of potential dilatation that may be made available during periods of increased cardiac work. The above disturbances also increase the work load on the heart by increasing the cardiac output and thus contribute in a secondary manner to the production of relative coronary insufficiency.

Hypotension. Decreased mean arterial pressure and, as a consequence, lowered diastolic pressure also results from any condition which lowers cardiac output. Included among such conditions are (1) hemorrhage, shock, excessive doses of the ganglionic blocking-drugs in hypertensive patients (Judson *et al.*, 1956), spinal anesthesia, and hyperthermia, all of which may lead to an inadequate volume of blood available to the heart in the central venous reservoir; (2) cardiac tamponade; and (3) acute heart failure from myocardial infarction. While the work of the heart is reduced in all these conditions, the head of pressure in the aorta may be reduced so much that the coronary flow is not adequate to supply the basal metabolic requirements plus that of the work being performed, and relative coronary insufficiency may develop.

Hypertension. Hypertension augments the work load on the heart but, fortunately, the elevated aortic pressure also increases the coronary flow directly, thus helping compensate for the increased need for coronary flow. In some hypertensive persons having an atherosclerotic aorta, however, the rigid aortic wall causes excessive elevation of systolic pressure without much elevation of diastolic pressure. In these persons the heart must develop a high pressure to complete ejection; nevertheless, during the major part of the cycle when most of the coronary flow occurs, i.e., during diastole, the aortic pressure is not proportionately increased. Indirectly, hypertension leads to insufficiency by increasing significantly the tendency to develop atherosclerotic narrowing of the coronary artery.

Aortic Valvular Stenosis. As a consequence of stenosis of the aortic valve, the work load of the ventricle is increased in order to create

* This is approximately the order of magnitude which we have observed.

the higher intraventricular pressure necessary to eject the blood through the narrowed aortic orifice. In this case, unlike hypertension, the aortic pressure is not elevated and consequently coronary flow is not proportionately increased. The need for increased coronary flow at rest can be met by arteriolar dilatation, but here again such dilatation limits the subsequent arteriolar dilatation that can occur with exercise.

Increased Work Demands, Elevated Heart Rate. Any factor which augments cardiac output increases the need for coronary blood flow. Such effect may occur in association with lowering of aortic pressure when drugs such as hydralazine are used in hypertensive patients (Judson *et al.*, 1956). An excessive heart rate also increases the need for coronary flow out of proportion to any associated increase in cardiac output. Of particular importance from the clinical point of view are exercise, eating of meals, chilling of the body and excitement. Extremely strenuous exercise, even in a normal person, can produce a demand greater than the coronary vessels can supply. In persons in whom coronary arteriolar dilatation is present at rest, this discrepancy between cardiac work and coronary blood supply occurs at much lower levels of cardiac work. Increased heart rate also shortens the time for diastole, relative to the cycle and, thereby, contributes to production of relative coronary insufficiency.

Myocardial Hypertrophy. Myocardial hypertrophy, in response to increased cardiac work, results in enlargement of the myocardial fibers. The number of capillaries is not increased, however, and as a consequence, the effective distance from the center of the myocardial fibers to the capillaries is increased, and the effective supply of oxygen and other nutrients per cubic millimeter of muscle fiber is reduced. With hypertrophy of significant magnitude, relative coronary insufficiency results, and this is one of the factors which limits effective hypertrophy.

Active Constriction of the Arterioles. It is well known that in the Raynaud phenomenon, excessive sympathetic vasomotor nerve discharges may cause the arterioles of the ex-

trémities to become unduly constricted, producing symptoms of inadequate circulation in the feet or hands. It has been proposed that a similar phenomenon may occur in the heart, *i.e.*, that pain impulses from the abdominal or thoracic viscera might reflexly induce a discharge of vasoconstrictor impulses to the coronary arterioles. Such activity might result in relative coronary insufficiency, especially in the presence of narrowing of the arteries. However, clear-cut evidence of the existence of such reflexes is lacking; and no evidence has been obtained of the presence of nerve fibers which are vasoconstrictor to the coronary arterioles.

Hypoxia (Anoxia). Even with a normal rate of flow, relative myocardial insufficiency may be caused by an anemic, an anoxic, or a cytotoxic (sodium cyanide) type of hypoxia. Since myocardial insufficiency is scarcely, if at all, induced by hypercapnia, the immediate participating factor is probably an inadequate oxygen supply *per se*, or the metabolic products resulting from such hypoxia.

PHENOMENA ASSOCIATED WITH CORONARY INSUFFICIENCY

Angina Pectoris. The pain of angina pectoris is usually felt under the sternum, but occasionally radiates to the neck or either shoulder or arm and occasionally to the epigastrium; it follows promptly the development of relative coronary insufficiency and disappears equally promptly upon relief of insufficiency. It rarely lasts more than a few minutes. The pain is analogous to the cramping pain which is felt in skeletal muscle when it is exercised during occlusion of the circulation to the muscle (Levis, 1932). Tissue activity appears to be more important than ischemia *per se* in the production of pain.

Afferent pathways for the pain impulses. The pain impulses are transmitted by way of the cardiac nerves and the sympathetic ganglia and enter the central nervous system by way of the lower cervical and the upper thoracic roots. Various theories have been proposed to explain the sites of radiation of the coronary pain; none of them is satisfactory. Radiation almost always extends to areas sup-

plied by somatic fibers which enter the spinal cord at the same level as do the afferent pain fibers from the heart.

Myocardial Contractility. *Loss of systolic shortening in the ischemic area.* A relative ischemia, such as can be produced experimentally by rhythmic occlusion and release of a coronary artery at half-second intervals or by coronary arteriolar constriction induced by an intracoronary injection of Pitressin, will cause a sequence of changes of contractility similar to those caused by complete occlusion.

Pulsus alternans. In the presence of relative coronary insufficiency, the refractory period of the affected muscle fibers is longer than normal so that these muscle fibers may contract only every other heartbeat. During the intervening beats, these muscle fibers are stretched. The resulting rhythmic alternation in the strength of the heartbeat and of the arterial pulse is called *pulsus alternans* (see Figure V-12).

Circulation in General. Practically no data are available regarding cardiac output during attacks of angina pectoris. Circulation time and venous pressure are unchanged. About 50 per cent of patients experiencing angina are hypertensives (Altschule, 1949).

Electrocardiographic Changes during Relative Coronary Insufficiency. The electrocardiogram shows nothing between attacks that is characteristic, although, of course, if a patient has hypertrophy or has had a previous coronary occlusion, changes characteristic of these lesions will be noted. However, during an attack of angina, electrocardiographic changes occur which are essentially the same as those seen during the early stages of coronary occlusion.

Tests for Latent Coronary Insufficiency. The two tests most frequently used in patients suspected of having anginal attacks are the exercise (step) test and the hypoxia (anoxia) test. These are designed to bring on a mild relative coronary insufficiency. In the two-step exercise-test, the patient is required to make a standard number of ascents, depending on his weight, age and sex. Electrocardiograms are taken immediately following the exercise (Master, 1950). If the RS-T seg-

ment is depressed more than 0.5 mm. below the base line, just before the beginning of the QRS complex in any lead, the test is regarded as positive (Russek, 1957).

In the hypoxia test, the patient breathes a mixture of 10 per cent oxygen and 90 per cent nitrogen for 20 minutes and electrocardiograms are taken at 5-minute intervals. If pain develops, the test is stopped immediately and 100 per cent oxygen is given. After the period of hypoxia, the patient breathes 100 per cent oxygen for 5 minutes and another tracing is then taken. Injection of epinephrine to increase cardiac work has also been employed to induce relative coronary insufficiency.

The "meal test" has also been advocated recently as a convenient method for testing patients suspected of having coronary insufficiency (Berman *et al.*, 1950). In this test, control electrocardiograms are taken, the patient is fed either a 1200-calorie or an 880-calorie meal, and 20 to 30 minutes later, a second electrocardiogram is taken. Abnormal changes in the T waves, exaggerated or inadequate increase in heart rate, depression of RS-T segment of 0.05 to 1.0 mm., premature ventricular contractions, and inability to increase the cardiac output adequately were noticed in cardiac patients, particularly in those having angina of effort. Often several of these changes were found in the same patient, while normal controls rarely showed any of these changes and almost never were more than one of them seen in the same person.

Relief and Prevention of Attacks by Reducing Work of Heart. Attacks of angina pectoris are usually relieved by decreasing the heart's work, as by cessation of exertion, avoidance of large meals, and changing from the horizontal to the vertical position. The nitrates which both relieve and prevent attacks are excellent dilators of the coronary arterioles; however, they may be effective because they also tend to cause a peripheral pooling of blood and a decrease in cardiac output. Gradual development of a collateral blood supply to a portion of the myocardium that is irrigated by a narrow coronary artery may lead to lessening the intensity, and even to disappearance, of anginal attacks.

Atherosclerosis. Angina pectoris and coro-

nary occlusion are usually associated with the occurrence of atherosclerosis. Prolonged hypertension significantly increases the frequency and severity of atherosclerosis of the coronary arteries. Atherosclerosis is intensified by the development of diabetes mellitus, and in women, is associated with the menopause (Goldstein *et al.*, 1956). No correlation has been noted between emotional stress and the development of coronary artery disease (Sprague, 1958).

Cause of Death. Death in patients with angina often results from noncardiac causes and occasionally from heart failure caused by non-coronary cardiac lesions. When it follows an anginal attack, death is usually sudden and probably initiated by ventricular fibrillation, since this irregularity has been noted in patients who in rare instances died while they were having electrocardiograms taken.

Coronary Occlusion

Sudden interruption of the blood flow in a coronary artery is usually caused by thrombosis or by hemorrhage into an atherosclerotic plaque. With rare exceptions, sudden occlusion is followed by myocardial infarction. Occlusion may also occur gradually as a result of progression of the atherosclerosis.

PHENOMENA ASSOCIATED WITH CORONARY OCCLUSION

Pain. The pain associated with coronary occlusion is identical in nature, and as far as is known, in mode of production, with that of angina pectoris. However, the pain is frequently more intense, may radiate more widely and always lasts longer, *i.e.*, hours to days. Radiation of the pain is more frequently to the left than to the right arm. Pain is present in 98 per cent of patients with coronary occlusion. Failure to obtain a history of pain may be explained by sudden onset of collapse, concealment by other symptoms or medication, or may not have been adequately sought.

In a series of 158 patients with coronary artery disease, Levy (1956) noted that the pain subsided in 18 per cent with bed rest, without producing significant myocardial necrosis. Remission

of pain associated with minor degrees of myocardial necrosis occurred in 40 per cent. The mortality rate after development of frank myocardial infarction was 16.5 per cent of the total group. Sixteen per cent of the entire group were classified in the category of "sudden unexpected death" without clinical or electrocardiographic evidence of significant myocardial infarction. He indicated that similar control data are required in evaluating anticoagulant therapy.

Myocardial Contractility. Normally the ventricular fibers shorten during ventricular ejection and lengthen during ventricular filling. Within 30 seconds after occlusion, the myocardial fibers cease shortening during systole. Within one or two minutes the myocardium in the ischemic area begins to elongate during systole. Maximum stretching is reached at the moment of peak of intraventricular pressure. The ischemic muscle fibers then shorten during diastole owing to their elastic recoil, while the normal fibers are being stretched by the inflowing blood. Loss of contractility has two effects: (1) loss of increment to the force of ejection which normally would have been provided by the ischemic muscle, and (2) bulging of the ischemic muscle during systole as a result of the force of ejection of the remaining active muscle.

Cardiac Rupture. With healing, the necrotic muscle fibers, which have lost their blood supply because of occlusion of a coronary artery, are replaced by firm scar tissue. Before scarring can occur, however, the pressure in the left ventricle during systole may force the blood to burrow through the necrotic myocardial fibers and eventually to rupture the wall. Perforation of the ventricular septum will allow blood from the left ventricle to enter the right ventricle. Perforation of the wall externally will force blood into the pericardial sac and lead rapidly to death from cardiac tamponade.

The influence of activity on the development of cardiac rupture is brought out by two comparative studies. Rupture was found in 9.5 per cent of 105 hearts with acute infarction at autopsy in hospitalized patients (Friedman and White, 1944); in contrast, rupture was found in 73 per cent of hearts of 22 patients who died from recent

infarcts in a mental institution in which the patients were not kept at bed rest (Jetter and White, 1944). In neither study were any instances of rupture encountered among 165 and 25 hearts, respectively, with old healed infarcts.

Collateral Circulation. Myocardial Necrosis. Frequently, at autopsy, one or more coronary arteries are found to be completely occluded, yet the myocardium customarily supplied by these vessels appears normal. Evidently either a collateral supply to this muscle had developed or the patient had died before myocardial necrosis had time to develop. A considerable period of time must elapse before collateral circulation becomes adequate to keep the muscle viable. Necrosis may thus be prevented if occlusion takes place gradually rather than suddenly, in order to allow time, and to provide the stimulus, for collateral circulation to develop (Baroldi *et al.*, 1956).

Circulatory Dynamics. A large infarction may be followed by acute left heart failure, associated with an elevated central venous pressure and decreased cardiac output per minute and per stroke. The output may, however, not be as low as in left ventricular congestive failure. Blood flow in the forearm is reduced, and intrathoracic blood volume and heart size are increased (Lee, 1957). Such patients respond to the administration of lanatoside C by a rise of systemic arterial pressure and, in some cases, also by a fall of venous pressure.

On the other hand, phenomena characteristic of a shock-like state may be seen during the first few hours or days. The symptoms of shock include low mean-arterial pressure, narrow pulse pressure, tachycardia, pallor, sweating, low venous pressure and diminished size of the superficial veins (venous constriction?).

Agress and associates (1950) found that the plasma and blood volume were reduced soon after the onset of myocardial infarction. The cause of the shocklike state is not known. It may be reflexly initiated by the pain impulses or it may be a direct result of the myocardial failure. In either case, the prolonged existence of severe hypotension leads to tissue hypoxia and critical

damage to the brain, myocardium and kidneys (Sampson, 1957). Fink and associates (1953) and Sampson (1957) believe that transfusion and/or the use of vasoconstrictors, such as phenylephrine or levarterenol (noradrenaline), improves such patients.

Cardiac Irregularities. Premature beats, tachycardias and especially ventricular fibrillation, which frequently follow coronary occlusion, are probably generated in the junctional area of partially ischemic muscle tissue between the infarcted and the surrounding normal myocardium. The "hyperirritability" of this area may be caused by catelectrotonus from the injury potential and possibly also by sympathoadrenal substances, histamine and other substances formed or liberated during necrosis (Harris, 1950), or induced by an electrical potential resulting from the differences in degree of oxygenation of adjacent portions of the myocardium. The enhanced irritability may be responsible for the origin of ectopic rhythms which lead to ventricular fibrillation (Brofman *et al.*, 1956).

Miscellaneous Associated Phenomena. Mild fever (100 to 101° F.), leukocytosis, an increased rate of blood sedimentation, and an elevation of serum glutamic oxaloacetic transaminase (GO-T), lactic dehydrogenase (LD) or glutamic-pyruvic transaminase (GP-T) (La Due, 1956, 1957) follow myocardial infarction. These are probably initiated by products absorbed from the necrotic myocardium. Creatinuria, nitrogen retention, jaundice, gastrointestinal disturbances and the shoulder-hand syndrome are occasionally encountered following occlusion. A mild pericarditis may develop over the surface of the infarct and give rise to a friction rub. Not infrequently, thrombi develop on the endocardium in the area of the infarct. These may become dislodged, giving rise to pulmonary emboli when they arise in the right atrium or ventricle, and to systemic emboli when they arise in the left ventricle.

Prognosis. In a follow-up study of 200 patients who had experienced a coronary occlusion between 1921 and 1930, the most important clue to longevity was the degree of complete recovery at the end of the first month

of convalescence; findings that indicated a shorter life span were persistence of either

congestive failure or angina (White *et al.*, 1958).

4. EXTRACARDIAC DISTURBANCES THAT AFFECT THE HEART

Disturbances That Interfere with Cardiac Filling

Angulation and Rotation of Heart. Angulation and rotation of the heart may occur during surgery on the heart or mediastinal structures, as a consequence of excessive pneumothorax (either accidentally or in the treatment of pulmonary tuberculosis), and as a result of infections which produce adhesions between the heart and chest wall. Such dislocations cause failure of filling or of emptying of the cardiac chambers by compressing the vessels as they penetrate the pericardium. As a result of the sudden displacement of the heart, systemic arterial pressure suddenly drops.

Traction on Heart. Traction has been given as the cause of hypertrophy in hearts that were bound by adhesions to various thoracic structures. However, traction in the longitudinal axis has no effect on cardiac output or systemic arterial pressure, and traction in other directions serves mainly to reduce cardiac output by narrowing the lumen of the vessels that enter or leave the heart. Hypertrophy is absent when the remainder of the heart is normal.

Acute Cardiac Compression (Cardiac Tamponade). *Dynamics.* Elevation of pericardial pressure by accumulation of air, blood, exudate or transudate within the pericardial sac tends to collapse the veins as they enter the pericardium, and also tends to collapse the heart chambers. The compression prevents proper ventricular filling and reduces cardiac output. The reduced output causes the systemic and pulmonary venous pressures to rise. The rise in systemic venous pressure is related to the available blood volume and to the degree of veno-constriction. Within limits, the elevation of venous pressures tends to compensate for the rising pericardial pressures and maintains cardiac filling and cardiac output. However, if the pericardial accumulation becomes excessive, the entering veins and

the cardiac chambers tend to collapse and the cardiac output becomes markedly reduced. The critical pericardial pressure at which cardiac output fails is around 10 to 18 cm. of saline (Nerlieh, 1951).

Distinction of massive pericardial effusions from large dilated hearts is possible on the basis of the arm-to-tongue circulation time (Bellett *et al.*, 1951). In the former, the time is less than normal or at most only slightly prolonged (8 to 22 seconds, average, 16 seconds in 17 patients), whereas with dilated hearts the circulation time would be expected to be markedly prolonged.

Pulsus paradoxus. Pericardial effusions of a magnitude less than that which causes failure of cardiac output frequently cause an accentuated decrease of mean arterial pressure and of the arterial pulsations in late inspiration or early expiration, and an increase in arterial pressure and pulsations in late expiration or early inspiration. These changes in pulsations, called the paradoxical pulse, appear to be caused by rhythmic intrathoracic pressure changes which have their normal effect on the central systemic veins and on the quantity of blood in the lungs but are unable simultaneously to affect the cardiac filling and output.

Clinical signs. The main findings in acute cardiac compression are falling arterial pressure, rising venous pressure and a small quiet heart. Associated with the elevated venous pressure may be enlargement of the liver and pulsation of the neck veins (Williams and Soutter, 1954). When caused by a perforating wound of the heart, the condition constitutes an emergency and often requires either immediate surgical intervention and closure of the perforation or pericardial aspiration (Farringer, 1955), since the heart continues to pump blood into the pericardial sac through the perforation as long as the heart is able to contract.

Pneumopericardium. In experimental animals, exposure of the heart or even of the

pericardium to atmospheric pressure raises the absolute pressure on the outside of the cardiac chambers (reduces the negative pressure to zero). This pressure change causes alterations in cardiac dynamics suggestive of mild cardiac compression (Beck and Cox, 1930).

Chronic Cardiac Compression (Constrictive Pericardium). The disturbance is produced by the contraction of the scar tissue and obstruction of the large veins as they enter the heart, and usually occurs long after the acute inflammatory process has subsided. The compression may be caused also by chronic accumulation of fluid. Primary amyloid infiltration of the myocardium may closely mimic the mechanical disturbances produced by constrictive pericardium (Gunnar *et al.*, 1955).

Cardiovascular effects of chronic cardiac compression. The effects produced by chronic cardiac compression are similar to those of acute cardiac compression. The compression causes (a) lowering of cardiac output because of inability of the ventricles to fill completely and (b) a resulting depression of systemic arterial pressure and elevation of systemic venous pressure. Because of the more prolonged nature of the disease, compensatory changes characteristic of those seen in chronic congestive heart failure develop. These include increase of blood volume (which may be as much as 1 liter above normal), and retention of salt and water with resulting enlargement of the liver, pleural effusion, ascites and dependent edema (Fishman *et al.*, 1950). Associated symptoms and signs are cyanosis, breathlessness, distended veins and pulsus paradoxus. The extent of the disturbances may vary greatly from patient to patient. Some may show predominantly congestive phenomena (hypervolemia), suggestive of myocardial insufficiency, and may respond to some extent to measures aimed at relieving the congestion (Harvey *et al.*, 1953).

Constrictive pericarditis over the left ventricle has been described by White and associates (1948). Their patients showed accentuated pulmonary second sounds, right ventricular enlargement, right axis deviation in the electrocardio-

gram and marked elevation of the pulmonary capillary pressure.

Cardiac work in presence of chronic cardiac compression. Contrary to conditions leading to chronic heart failure, the work of the heart is reduced in cardiac compression and the heart atrophies. Fluoroscopic examination reveals decreased cardiac action. Surgical excision of the constricting pericardium often greatly improves this type of cardiac disturbance (Holman and Willett, 1955).

Ball-Valve Thrombus. A rather rare condition which may lead to impairment of cardiac filling is a free floating or a pedunculated ball-valve thrombus. Such thrombi have been noted most frequently in the left atrium in the presence of mitral stenosis, and in the right atrium in the presence of chronic cardiac compression combined with atrial fibrillation. Thrombi within the four cardiac chambers are quite common but, fortunately for the patient, they rarely assume the ball-valve form.

Ball-valve thrombi in the atria may offer a constant impediment to ventricular filling, thus resembling mitral or tricuspid stenosis, or they may occlude the opening only periodically. Periodic occlusion causes sudden attacks of syncope, decreased cardiac output and feebleness of the pulse. When present in the right atrium, the patient may show dusky cyanosis of the face and neck, engorgement of veins of the face and neck and of the liver with a systolic pulsation in these structures, marked dyspnea of the oxygen-hunger type without signs of respiratory obstruction, enlargement of the right atrium, evidence of old rheumatic heart disease, atrial fibrillation, a murmur suggesting tricuspid stenosis, and rapid fluctuations in severity of symptoms over short periods of time.

Asthma, Pneumothorax and Pleural Effusion. These often cause a mild elevation of the central systemic venous pressure, measured relative to atmospheric pressure. The elevation is related to the increase in absolute pressure in the thorax (intrathoracic pressure is less negative) which impairs to some extent the return of blood to the heart. Few

measurements of cardiac output are available but these suggest little deviation from normal conditions while at rest (Altschule, 1949).

Explosive Decompression. In the pressurized cabin of an airplane, the air pressure within the cockpit or cabin is maintained at the equivalent of no more than 10,000 feet altitude. An anti-aircraft shell can make a large hole in the wall of such a cabin. If the hole should develop when the airplane is flying at 40,000 feet, the pressure in the cabin would drop suddenly from 522 to 140 mm. Hg. This drop may take place within 0.005 to 0.2 second, and the phenomenon is, therefore, designated explosive decompression.

Normally man and animals readily tolerate explosive decompression but, if the degree or the rapidity of change is great enough, the arterial pressure may decline momentarily principally because the intrathoracic pressure is maintained for the time being at around 522 mm. Hg while the rest of the body is exposed to a pressure of 140 mm. Hg. This produces the effect of mild tamponade equivalent to that seen in emphysema or pneumopericardium. The effect is aggravated by increasing the altitude of the plane at the time of decompression and by shortening the time of decompression (Gagge and Shaw, 1950). Any resistance to expiration, such as spasm of the glottis, aggravates the effect since such resistance delays the drop in intrathoracic pressure (Beoke, 1950).

If the altitude of the plane at the moment of explosive decompression is above 75,000 feet, more severe symptoms may ensue, since at this altitude body fluids tend to boil and extreme distention of all bodily tissues occurs. In experimental studies on monkeys, exposed to decompression equivalent to 75,000 feet in 0.2 second, cessation of respiration, bradycardia, reduction of systemic systolic and diastolic arterial pressures and disruption of the normal electrocardiogram were observed. When breathing of 100 per cent oxygen was begun immediately and the monkeys were recompressed at the free fall rate (in approximately 5 minutes), they began to recover and their arterial pressures, respirations and electrocardiograms were normal by the time sea-level pressure was reached (Gelfan *et al.*, 1950).

Disturbances Affecting Primarily the Pulmonary Circulation

ACUTE COR PULMONALE

Pulmonary Embolism. Three forms of response to pulmonary embolism have been distinguished: (a) sudden death (usually attributed to coronary occlusion), caused by an embolus involving a major branch of a pulmonary artery; (b) subacute illness, resembling terminal bronchopneumonia, which may result from involvement of large and medium-sized arteries; and (c) chronic disease, usually incident to prolonged terminal illness, in which frequently only the small arteries are occluded (Towbin, 1954).

Circulatory dynamics during pulmonary embolization. Serious obstruction to the blood flow in the pulmonary arteries probably occurs only when emboli occlude 50 per cent or more of the pulmonary arterial system. The impediment to flow causes retention of blood in the right ventricle, rise of right atrial and right ventricular initial pressures, increased force of right ventricular ejection and elevation of the pressure in the proximal segment of the pulmonary trunk. The mean and pulse pressures decline in the segments of the pulmonary artery distal to the emboli. If right ventricular output fails to be maintained, left ventricular output falls and this causes syncope or a shock-like state with peripheral vasoconstriction. Severe tachycardia (Renner, 1949) or atrial flutter or fibrillation, a systolic murmur, an accentuated second sound, and a to-and-fro rub in the pulmonic area may result.

Pulmonary air embolism. Durant and associates (1947) studied the phenomena of pulmonary air embolism in dogs. They found that the amount of air needed to cause death varied widely depending upon the speed of injection, the position of the dog and the ability of the animal to eliminate the air lodged in the pulmonary capillaries by developing tachypnea.

Ligation of Pulmonary Artery. In pneumonectomy, ligation of the corresponding pulmonary artery usually causes an immediate elevation of the pulmonary arterial pressure.

The pressure, however, usually returns to basal levels by the time the operation is completed.

Elevation of Pulmonary Capillary Pressure. Elevation of the pulmonary capillary pressure usually results from failure of the left ventricle or from mitral stenosis. The elevation may be brought on acutely by any factor which suddenly increases the systemic venous return, such as infusions, exercise or dreams. Pulmonary capillary pressure may also be increased by sudden elevation of the systemic arterial pressure by large injections of epinephrine, the physiologic output of epinephrine that accompanies ischemia of the central nervous system, or inhalation of oxygen at high pressure (Bean and Johnson, 1955).

Rises in mean pulmonary arterial pressure and pulmonary capillary pressure have been recorded in normal persons receiving one liter of physiologic saline solution intravenously within 10 minutes, and were regarded by Warren and associates (1950) as a "back pressure" effect.

CHRONIC COR PULMONALE

Chronic Pulmonary Disease (Pulmonary Fibrosis, Emphysema, Ayerza's Syndrome). Insofar as the heart is concerned, most chronic pulmonary diseases may be grouped together. They are all associated with cyanosis resulting from increased unsaturation of arterial oxygen produced by ineffective alveolar ventilation (Comroe and Fowler, 1950) and the associated polycythemia. In the absence of heart failure, pulmonary arterial systolic and diastolic pressures, pulmonary artery-pulmonary "capillary" pressure gradient (Yu *et al.*, 1955) and right ventricular systolic and right atrial pressures are usually elevated at rest (Borden *et al.*, 1950), and increase excessively with slight exercise. The blood volume is increased but cardiac output, arteriovenous oxygen difference and systemic arterial pressure are usually normal (Hecht, 1956).

The elevated pulmonary artery pressure at rest is caused by constriction and possibly also by some obstruction of the small arteries of the lungs (Leopold, 1950). The constriction may be related to the anoxia since short pe-

riods of anoxia cause acute elevation of the pulmonary arterial pressure and pulmonary arteriolar resistance, as computed from the relationship between pulmonary artery-pulmonary "vein" pressure and cardiac output (Siebens *et al.*, 1955; Ebert, 1957).

Heart failure associated with cor pulmonale is often, but not always, accompanied by a resting cardiac output above normal and by excessively elevated mean pulmonary arterial and right ventricular systolic and diastolic pressures. The results of therapy also suggest that this kind of heart failure is of the high-output type and may be associated with constriction of small pulmonary arteries, which is reversible (Cournaud, 1950).

Pulmonary Hypertension Secondary to Mitral Stenosis. Pulmonary artery mean pressure may be elevated to 30 to 50 mm. Hg or more in the presence of mitral stenosis. Associated with this condition are radiologic evidence of right ventricular hypertrophy, changes in the electrocardiogram in lead V, and pulmonary edema (Fowler *et al.*, 1955). In most patients the pulmonary "capillary" pressure (pulmonary artery wedge pressure) and the gradient between pulmonary artery and pulmonary "capillary" pressures are both elevated.

Disturbances Affecting Primarily the Systemic Circulation

CONDITIONS CAUSING INCREASED RESISTANCE TO BLOOD FLOW

Hypertension. *Increased peripheral resistance in hypertension.* It is generally agreed that in systemic arterial hypertension cardiac output is normal but total peripheral resistance is increased. A large number of causes have been proposed for the increase in peripheral resistance in human hypertension. It is beyond the scope of this chapter to discuss them.

Aortic pressure in hypertension. In order to overcome the increased resistance to flow of blood through the systemic arterioles, the heart must create a higher pressure in the aorta and systemic arteries. The higher arterial pressure leads to a greater than normal cross-sectional area of the aorta, in which

condition it is less distensible than normal. As a consequence of the greater rigidity of the aorta, the pulse pressure is wider than normal even though the stroke volume output of the heart is within normal limits.

Effects of hypertension on the heart. The elevation of arterial pressure causes increased left ventricular work and leads to left ventricular dilation and hypertrophy and to an accentuated aortic second sound. Right ventricular pressure usually remains normal in the absence of complications but may rise in patients with the malignant type of hypertension. Coronary blood flow increases with the rising of arterial pressure. Elevation of the systemic arterial pressure predisposes to atherosclerosis and thereby increases the likelihood of thrombotic complications in vessels such as the arteries of the brain, heart, kidneys and lower extremities.

Polycythemia. Increases in the concentration of red cells in the blood, in the hematocrit reading, in the oxygen-carrying power of the blood, and in the total circulating blood volume occur as a physiologic response to many kinds of anoxia (secondary polycythemia). Increased red cell counts and hematocrit readings are also seen in polycythemia vera in which no cause for the increased quantity of red cells can be demonstrated.

In both kinds of polycythemia the blood becomes much more viscous, the resistance to flow through the arterioles and capillaries being greatly increased. The increased viscosity is to some extent compensated by peripheral arteriolar vasodilation. The latter causes, in turn, capillary dilatation and the associated red blush of the skin (Jeghers, 1950). Despite the peripheral vasodilation, there may result moderate systemic hypertension, increased cardiac work and moderate cardiac hypertrophy (Brooks, 1936).

Effects of Excessive Quantities of Sympathetic Chemical Mediators. *Causes of excessive blood concentration of sympathomimetic substances.* Epinephrine is released from the adrenal gland and arterenol is released at the terminals of the postganglionic sympathetic fibers in the tissues during activity of the

sympathetic nervous system. These substances are not completely destroyed in the tissues. As a consequence, they diffuse into the blood and are thus capable of exerting sympathomimetic effects in other parts of the body. The quantity of these substances reflects the activity of the sympathetic nervous system. Excessive quantities of sympathetic chemical mediators may be present in the body as a result of accidental injection of abnormally large doses of epinephrine, or as a physiologic response to conditions of extreme stress such as development of shock, severe anoxia, presence of a pheochromocytoma, or severe ischemia of the central nervous system, and as a result of loss of the moderator impulses from the pressor receptors in the carotid sinuses and aortic arch.

Effects of injection of excessive quantities of epinephrine in man and experimental animals. Accidental injections of large amounts of epinephrine into patients may lead to precordial distress, increase of sedimentation rate, elevation of body temperature, and electrocardiographic changes suggestive of relative coronary insufficiency. Epinephrine may occasionally induce ventricular premature beats, tachycardia or fibrillation; these are particularly likely to occur during chloroform or cyclopropane anesthesia.

Experimental neurogenic hypertension. Moderate increase of sympathetic tone occurs in experimental neurogenic hypertension induced by sectioning the afferent moderator nerves from the carotid sinus and aortic arch. In experiments of this type, it was noted that cardiac output rose, arteriovenous oxygen differences and coefficient of oxygen utilization both decreased, and heart rate increased, but stroke volume and right atrial pressure remained unchanged. Blood flow in the kidney fell while that in the forepaw rose (Bing *et al.*, 1945)

EXCESSIVE CARDIAC OUTPUT CAUSED BY ABNORMALLY INCREASED VENOUS RETURN

Increased venous return in normal hearts causes no difficulty. A sudden increase in venous return can, however, throw a dam-

aged heart into acute heart failure, usually of the left ventricular type. Associated with the failure will be increased pulmonary blood volume, elevated systemic and pulmonary arterial and systemic central and peripheral venous pressures, and increased cardiac and respiratory rates. The difference between peripheral and central systemic venous pressures will be reduced (Huckabee *et al.*, 1950). In the absence of failure, increased venous return induced by infusions usually leads to increased renal blood flow and glomerular filtration and to efferent renal arteriolar dilatation as represented by a reduced filtration fraction (Wilson and Harrison, 1950).

INCREASED CARDIAC OUTPUT FROM EXCESSIVE DECREASE IN PERIPHERAL RESISTANCE

Peripheral Vasodilatation Associated with Increased Metabolic Rate. The metabolic rate of the body, as indicated by measurement of oxygen consumption, is increased physiologically in exercise, after meals, and during pregnancy, and in obesity, hyperthyroidism and during fever.

Pregnancy. Cardiac output begins to increase early during pregnancy and reaches a peak of around 20 to 25 per cent above normal at about the thirty-second week, it returns to normal near term. A second marked increase in cardiac output occurs during the first and second days postpartum. In the presence of a damaged heart, heart failure is most likely to occur about the thirty-second week or the immediate postpartum period when cardiac output is highest. Occurrence of infection at any time during pregnancy, and especially during the above periods, increases still further the need for blood flow and the likelihood of development of heart failure (Jenson, 1949). However, no permanent change in the degree of heart disease attributable to the pregnancy was detected when mothers were re-examined 3.5 to 5 years postpartum (Miller and Metcalf, 1956, Leiter, 1957).

Fever. In general, heart rate and oxygen consumption parallel the body temperature. Heart rate increases about 20 beats per minute per degree (Centigrade) of fever. The

increased rate seems to be largely a direct effect on the sinoatrial node. In heart block the heart rate increases only about 8.4 beats per minute per degree Centigrade (Altschule and Freedberg, 1945). During fever induced by intravenous injection of pyrogenic substances, three stages with distinctive circulatory characteristics may be noted. In the prodromal stage there are no appreciable changes. A stage of chilling follows in which cardiac output is below normal. Flushing then occurs during which cardiac output, heart rate, stroke volume, and oxygen consumption are elevated above normal. Enlargement of the heart may be noted during, and for as long as six months following, prolonged artificial hyperpyrexia.

Exercise. Physical exertion induces the greatest possible increase in cardiac output. The increased output is caused both by a faster heart rate and by an augmented stroke volume. In persons in good physical condition, the latter is the more important. The systemic arterial systolic pressure and the pulse pressure increase and the diastolic pressure remains relatively constant. The arteriovenous difference in oxygen concentration usually increases slightly (Bruce *et al.*, 1949a, b). In the injured heart, the increased venous return and the increased demand for output may readily exceed the capacity of the heart, leading to ventricular dilatation and failure. In the normal person, prolonged heavy exertion apparently does not lead to significant dilatation, but evidence exists that the heart may hypertrophy (Abrahams, 1946). The work of the heart may be increased more by anxiety than by moderate exercise (Stevenson *et al.*, 1949).

Meals. Ingestion of a large meal increases cardiac output and heart work 30 to 40 per cent. The increase begins almost immediately and is maintained for 3 or more hours. A high protein meal causes the greatest increase. Carbohydrate causes a lesser increase which is of shorter duration; fat causes a still smaller increase in cardiac output, but the output remains elevated for a longer period of time. Ingestion of 1200 ml. of water may increase cardiac output 15 to 25 per cent.

Increased Cardiac Output in Absence of Elevated Metabolic Rate. Arteriovenous fistulae. Arteriovenous fistulae frequently develop as a result of trauma, gunshot or knife wounds involving the femoral or abdominal vessels. The flow through the shunts greatly augments the venous return and the cardiac output, and decreases the arteriovenous-oxygen difference to less than normal. When the cardiac output is large enough, hypertrophy develops. The degree of hypertrophy is directly related to the size of the fistulous opening and to the proximity of the opening to the heart. The hypertrophy is at least partially reversible when the shunt is closed (Shumacker and Stahl, 1949).

Occlusion of the shunt, by application of external pressure, in man, causes immediate reduction in cardiac output and, conversely, cardiac output increases within 1 or 2 beats after re-establishing the shunt. This suggests that arterial pressure *per se* plays an important part in regulating the stroke volume of ejection of the left ventricle. The central venous pressure tends to remain constant during opening and closing of the shunt. While systemic arterial pressure tends to fall when the shunt is opened, the fall to a considerable extent is compensated by the increased cardiac output and by peripheral vasoconstriction (Stead and Warren, 1947; Van Loo and Heringman, 1949).

Osteitis deformans (Paget's disease of bone). This condition is associated with increased cardiac output, amounting at times to as much as 13 liters per minute, because of increased flow through the bones, and is often accompanied by a pronounced degree of atherosclerosis. Like pregnancy, this condition is closely analogous to arteriovenous fistula. However, recent cardiodynamic studies have questioned the occurrence of heart failure on the basis of the arteriovenous communications *per se* (Leiter, 1957).

Stress of life (Neurocirculatory asthenia, Anxiety). As a part of the reaction to stressful situations of life, especially in persons who are subject to tension, frustration, conflict, anxiety and depression, the cardiovascular system may react dynamically. Usually these reactions in such persons at rest are of the hyperdynamic type that is characteristic of

the normal response to exercise; they occur more in response to threatening than to actual assault upon the organism. Occasionally, hypodynamic reactions occur, particularly in healthy persons, when they feel depressed by some environmental situation. The hyperdynamic responses include fluctuations in rate and rhythm (such as paroxysmal tachycardia) and in strength and amplitude of cardiac contraction (increased stroke volume). The condition is characterized by an increase above normal in cardiac output (cardiac index averaged 5.5 with a normal output of 3.3 l./min./sq.M.) despite a normal rate of oxygen consumption. In consequence, the arteriovenous oxygen difference is reduced from the normal of 4 to an average of 3.2 ml. per 100 ml. of blood (Stevenson *et al.*, 1949; Wolff, 1950).

HYPOXIA

Respiratory Hypoxia. Low atmospheric oxygen tension. While breathing oxygen at less than normal concentration, the arterial blood pressure, cardiac output and heart rate increase but the oxygen uptake by the lungs remains constant. If the oxygen concentration of the inspired air is lowered progressively, cardiac failure ultimately ensues with rapid decline in arterial pressure, decrease of oxygen uptake and dilatation of the heart (Feldman *et al.*, 1948). Coronary blood flow increases remarkably in response to respiratory anoxia, prior to cardiac failure, accompanied by a marked increase in difference of oxygen concentration between the aorta and coronary sinus (Hackel *et al.*, 1954).

Contrary to general opinion, Craybiel and associates (1950) found the size of the heart to be decreased in all normal persons during partial acclimatization to high altitude, because of decreased filling. However, they state that life-long residents at high altitudes have hearts larger than normal.

Gassing by pulmonary irritant. Phosgene poisoning leads to pulmonary edema, which in turn, causes lowering in oxygen saturation of the arterial blood. The latter is the primary cause of death. Accompanying phenomena are prolonged pulmonary circulation

time, increased arteriovenous oxygen difference, hemoconcentration, decreased blood volume and increased blood viscosity. However, systemic venous and right ventricular pressures tend to remain constant or to fall (Patt *et al.*, 1946).

Anemia. In anemia, whether normochromic, hyperchromic or hypochromic, symptoms are produced which are more or less proportional to the oxygen-carrying power of the blood. No consistent changes in cardiac output are noted when the hemoglobin is above 7 grams per 100 ml. Below this level cardiac output is increased, arteriovenous difference in oxygen concentration and peripheral resistance are reduced, but right atrial pressure is unchanged (Brannon *et al.*, 1945). In severe anemia (hemoglobin concentration below 25 per cent of normal), right atrial pressure, cardiac output, stroke volume, heart rate and pulse pressure are greatly increased, even at rest, despite reduction of blood volume to as little as 2 liters (Sharpey-Schafer, 1944). The heart may become extremely dilated with functional insufficiency of the mitral and tricuspid valves and the appearance of "hemie" murmurs (Hunter, 1946); congestive failure may develop.

Stagnant Hypoxia. Shock. Most instances of true or "irreversible" shock go through an initial stage of decreased blood volume, leading to decreased cardiac output and extreme arteriolar vasoconstriction (both neurogenic and humoral in origin). Ultimately these changes lead to such severe tissue anoxia that the capillaries become damaged with resulting dilatation, increased permeability and stagnation.

Histotoxic Hypoxia (Cyanide Poisoning). Injection of a coronary artery with sodium cyanide causes marked coronary arteriolar dilatation and increase of coronary blood flow. When injected intravenously in man, sodium cyanide in doses of 0.1 to 0.2 mg. per kilogram, has caused a sinus pause of 0.88 to 4.2 seconds followed in some cases by nodal escape. The pause immediately preceded or accompanied the respiratory stimulation. Sinus irregularity and slowing of the heart rate then ensued, followed by a gradual acceleration above control levels.

Disturbances Affecting Primarily the Heart

INFECTIONS OF HEART

Myocarditis. Mild damage to heart muscle has been reported with subacute bacterial endocarditis, syphilis, scarlet fever, pneumonia and other infections. Prolonged arterioventricular conduction or varying grades of intra-ventricular block and significant RS-T deviations may be noted (Fine *et al.*, 1950). Virus infections rarely cause myocardial damage.

Invasion of the myocardium has been noted with trichinosis (Gould, 1945) and trypanosomiasis, and these may lead to myocardial weakness or, rarely, to failure. Extensive replacement of the myocardium by granular fibrous tissue, characteristic of sarcoidosis, was found in a 47-year-old white man who died suddenly (Stephen, 1954). Ten cases of cardiac hypertrophy and rapidly progressing, fatal, myocardial failure of unknown origin were described by Elster and associates (1955). At necropsy the hearts of the patients showed striking hypertrophy, degenerative muscular changes, and subendocardial and endocardial focal areas of necrosis and fibrosis frequently associated with mural thrombi. No other significant abnormalities were found.

Rheumatic fever and occasionally scarlet fever cause acute myocardial weakness which may lead to cardiac dilatation and death from subacute heart failure, with associated engorgement of the liver and abdominal viscera, but apparently with minimal dyspnea. The patient may experience mild precordial discomfort or occasionally may have actual angina and palpitation. Physical examination may reveal murmurs which usually, in the acute stage, are caused by functional valvular insufficiency resulting from the cardiac dilatation, but these changes are relatively uncommon in young adults. Murmurs may, of course, also be present because of structural damage from previous attacks of rheumatic fever. The phonocardiographic recording of the murmurs reveals, in most patients with myocarditis, a deflection in early diastole representing vibrations which may or may not be audible and which may represent either murmurs or a third heart sound (Buslmer *et al.*, 1954). The electrocardiogram may show sinus tachycardia, premature beats, prolonged P-Q interval (0.21 to 0.25 sec.), atrial fibrillation, intra-ventricular block and either left or right axis deviation.

More commonly, acute infections, and particularly diseases such as Rocky Mountain spotted fever, typhus fever and typhoid fever, are associated with peripheral circulatory failure or what might be called medical shock. In these diseases the impairment of cardiac output results from decrease of effective blood volume caused by increased capillary permeability and stasis rather than direct impairment of myocardial contractility (Harrell and Aikawa, 1949).

Pericarditis. Acute pericarditis may lead to acute inflammatory changes, usually involving the epicardium and the outer layers of the myocardium. The pericarditis may result in effusion and produce acute compression, or it may ultimately cause chronic cardiac constriction through contraction of scar tissue. Acute fibrinous pericarditis occurs most often during acute rheumatic fever, but may accompany upper respiratory infections, pneumonia, influenza, tonsillitis, tuberculosis or uremia, and at times may occur without apparent cause. Chronic cardiac compression resulting from acute pericarditis has occasionally been reported. The following characteristics help to distinguish pericarditis from coronary occlusion: (1) Fever, a friction rub and an increased sedimentation rate tend to occur on the first day with acute pericarditis (Levy and Patterson, 1950). (2) pain is usually present (noted in 46 of 50 cases reported by Carmichael and associates, 1951), but its location in pericarditis is highly variable, and it is intensified by respiration, cough or change of position; (3) the myocardial damage in pericarditis is diffuse, whereas in infarction resulting from arterial occlusion it is sharply localized.

Endocarditis. In a survey of 76 fatal cases of subacute bacterial endocarditis (Saphir *et al.*, 1950), various combinations of inflammation, perivascular infiltration, Aschoff bodies, infarcts and intravascular emboli were found in the myocardium. Tachycardia, presumably caused by fever, was present in 23, and various types of premature beats in 23 instances. Twelve patients showed delay in atrioventricular conduction, and 4, intraventricular block. Seventy-five per cent of 61 patients from

whom serial electrocardiograms were taken showed progressive changes.

MECHANICAL DISTURBANCES

Trauma. Demonstrable evidence of cardiac damage has been found in persons with serious accidental trauma to the body. The myocardial damage may be associated with precordial discomfort or slight dyspnea. In many instances gallop rhythm, pericardial friction rub and various systolic murmurs are noted momentarily. In a few instances, the electrocardiograms show evidence of pericardial or myocardial involvement but only rarely is the damage permanent. Desforges and co-workers (1955) reported successful suturing of the right atrium which had been ruptured by trauma.

Funnel Chest. Funnel chest or pectus excavatum may be hereditary or, rarely, may follow injury. It results from posterior displacement of the sternum in relation to the lower anterior chest wall which maintains its normal position. Serious cardiac embarrassment is rare, although palpitation and dyspnea may be noted after exercise.

METABOLIC DISTURBANCES

Hyperthyroidism. Thyrotoxicosis results from excessive production of the internal secretion of the thyroid gland. The increased secretion stimulates the metabolic rate of most organs of the body; the need for blood flow may be as much as 50 per cent above normal at rest. The disproportion may be even greater during exertion. The demand for increased blood flow results in an increase in heart rate, stroke volume and cardiac output, a slight increase in mean arterial pressure and a considerable widening of the pulse pressure and a bounding pulse. The demand for increased work leads to cardiac dilatation and hypertrophy. Atrial fibrillation frequently accompanies thyrotoxicosis and, when it does, it adds to the burden of the heart (Griswold and Keating, 1949). The thyroid secretion also acts specifically on the heart itself, directly stimulating its metabolism (Coh and Daliem, 1957). Hyperthyroidism increases the sensitivity of the heart to sympathetic stimulation

and decreases its sensitivity to vagal stimulation (Hoffman *et al.*, 1947). This change in sensitivity to epinephrine probably accounts in part for the tachycardia in hyperthyroidism.

Catheterization studies of patients, before and after treatment for hyperthyroidism, reveal that the excess thyroid hormone caused increased myocardial oxygen consumption and induced coronary arteriolar dilation, the degree of these changes being roughly proportioned to the increased heart rate and work (Rowe *et al.*, 1954; Leiter, 1957).

The condition may be severe enough to lead to congestive failure, especially in the presence of valvular vascular deformities or when atrial fibrillation develops. The presence of thyrotoxicosis in patients with atrial fibrillation makes it exceedingly difficult to control the rapid ventricular rate by digitalis.

Hypothyroidism. Pulse rate, plasma volume, velocity of blood flow and vital capacity are low. Venous pressure is approximately normal. The cardiac output and the work of the heart are decreased below normal, the decrease being relatively greater than that of the oxygen consumption, so that the arteriovenous oxygen difference is above normal. The heart is generally enlarged and the mean arterial pressure is slightly elevated but the pulse pressure is less than normal. Pericardial effusion may be present. The bradycardia of hypothyroidism is caused by changes of sensitivity of the adrenergic and cholinergic heart effectors to the respective neurotransmitters (Hoffmann *et al.*, 1947).

Cardiac catheterization reveals normal cardiopulmonary pressures, even when the hearts are enlarged and the electrocardiograms abnormal. In 2 persons, cardiac output was reduced out of proportion to the low oxygen consumption, and right ventricular and pulmonary artery pressures rose on exercise, but these patients were in the atherosclerotic age group (Leiter, 1957). The oxygen consumption per milligram of isolated atrial and ventricular myocardium from hypothyroid animals is decreased 25 per cent below that from normal animals (Coh and Dallam, 1957). Since the work of the heart in hypothyroidism is apparently decreased both at work and in exercise, creation of a mild state of hypothyroidism

has been recommended in congestive heart failure.

Functioning Carcinoid Tumors (Hyperserotoninemia). Carcinoid tumors are believed to originate in the secretory chromaffine cells of the intestinal tract, principally in the lower third of the small intestine. The malignant tumors usually metastasize to the liver. These cells produce serotonin (5-hydroxytryptamine) which is converted to 5-hydroxyindol-acetic acid and excreted in the urine. Cardiovascular phenomena associated with malignant carcinoid tumors having metastatic growths, presumably caused by excessive formation of serotonin, include (a) fibrotic changes in the endocardium of the heart, principally on the right side with accompanying pulmonary stenosis; and (b) dilatation of the capillaries, venules and small veins of the skin with associated miliary and gross telangiectasia and mild thickening of the skin. These disturbances lead to right-sided heart failure with progressive exertional dyspnea, fatigability, dependent edema and preterminal signs of pulmonary and tricuspid valvular lesions (Mattingly and Sjoerdsma, 1956).

Disturbances of Plasma Electrolyte Levels, Hyperpotassemia. Hyperpotassemia has been produced by administration of 2 to 6 Gm. of potassium iodide per day, in the treatment of syphilis and in patients with uremia. Serum potassium levels as high as 10.5 mEq./l. have been recorded (normal about 5 mEq./l.) during which time the patient may develop acute uremia with oliguria, recurrent nausea, episodes of bradycardia with symptoms of heart failure, and sudden ascending quadriplegia without paralysis of trunk or disturbance of speech or mental function (Finch and Marchand, 1943). The heart may have sinus tachycardia, supraventricular paroxysmal tachycardia or complete A-V dissociation with irregularities suggesting ventricular fibrillation.

Hypopotassemia. Marked lowering of serum potassium from the normal of about 20 mg./100 ml. (5 mEq./l.) to 3 to 11 mg./100 ml. (0.6 to 2.8 mEq./l.) occurs during attacks in family periodic paralysis, and as a result of loss of potassium in chronic nephri-

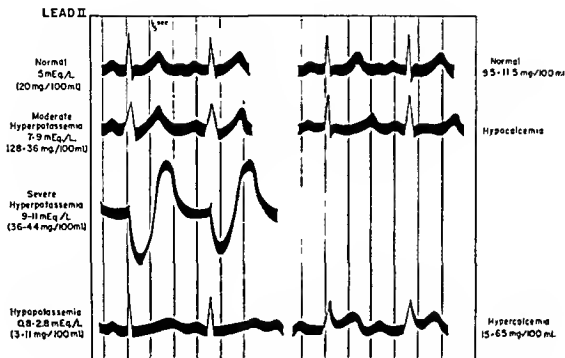


Figure V-13 Schematic diagram of changes in electrocardiogram resulting from abnormal concentration of electrolytes.

tis, in overtreatment of adrenal cortical insufficiency with desoxycorticosterone, and occasionally during treatment of diabetic acidosis. Clinical symptoms accompanying the hypokalemia include skeletal muscular weakness and paralysis which are more marked in the lower extremities and are accompanied by pain and stiffness in the muscles. Potassium excretion is not increased during the attacks of periodic paralysis; the attacks subside spontaneously. The only cardiovascular manifestations are those seen in the electrocardiogram (Figure V-13).

Hypocalcemia. Only electrocardiographic changes are noted (Figure V-13).

Hypercalcemia. During continuous intravenous infusion of calcium chloride into morphinized or barbitalized dogs, various degrees of A-V block and atrial fibrillation are observed. These changes occur at calcium concentrations ranging from 15 to 65 mg/100 mL (Hoff *et al.*, 1939). (See Figure V-13.)

Elevated levels of magnesium. Magnesium injected intravenously into anesthetized dogs, at levels below 5 mEq/L, causes an initial drop in arterial pressure, followed by depression and failure of respiration at levels of 15 to 17 mEq/L. (Smith *et al.*, 1939).

Thiamine Deficiency. Beriberi heart, Beriberi heart disease is characterized by enlarged heart with normal sinus rhythm, dependent edema, elevated venous pressure, peripheral neuritis or pellagra, nonspecific changes in the electrocardiogram, no other evident cause of heart disease, gross deficiency of diet, and by improvement with use of thiamine. The cardiovascular aspects of beriberi primarily result from the myocardial disturbance caused by the thiamine deficiency. The physiologic changes in heart failure from beriberi are associated with reduced production of myocardial energy, the proper completion of carbohydrate metabolism in the citric acid cycle being prevented by a block between pyruvate and acetyl coenzyme A. The utilization of pyruvate and lactate by the myocardium is impaired, as is fatty acid catabolism. Myocardial extraction and consumption of oxygen are reduced (Leiter, 1957).

Amyloidosis. Gargoylism. Hemochromatosis. Muscular Dystrophy. Diffuse or nodular myocardial deposits, and infiltration of the visceral pericardium, endocardium or coronary artery with amyloid may be severe enough to lead to myocardial failure or may

mimic constrictive pericardium; amyloid deposits in the lungs may lead to *cor pulmonale*. The amyloid may be limited to the heart or the cardiac deposits may be associated with systemic amyloidosis. *Gargoylism* (lipochondrodystrophy) is a rare condition that is evident in infancy. Among other manifestations, it may reveal nodular thickening with gelatinous material in the valves, especially the mitral, and in the coronary arteries. Death may result from chronic congestive heart failure. *Hemochromatosis* may be associated with enlargement of the heart and deposits of iron pigment in the myocardial fibers and may be accompanied by cardiac arrhythmias and conduction disturbances and heart failure. *Muscular dystrophy* may be associated with myocardial involvement in about half the cases, with evidence of interstitial fibrosis and massive scars in the myocardium, leading to cardiac failure (Leiter, 1957).

Chronic Malnutrition. Endomyocardial Fibrosis. Cardiac atrophy may be associated with various types of emaciation. Heart failure is rarely manifested during the wasting, but acute heart failure may appear during sudden attempts at renutrition. *Nutritional heart disease*, characterized by a low cardiac output, has been observed in adult urbanized Bantus of South Africa who live on a high carbohydrate, very low protein diet. *Endocardial fibrosis*, a nutritional disease which is responsible for 15 per cent of deaths from congestive heart failure in natives of Uganda (East Africa), is associated with mitral and occasionally tricuspid insufficiency, and endocardial fibrosis of both ventricles with subendocardial myocardial necrosis and organizing mural thrombosis (Leiter, 1957).

Some patients with muscular dystrophy have been shown by catheterization studies to be on the verge of congestive heart failure (Gailani *et al.*, 1958).

Hypothermia. In dogs and guinea pigs, lowering of body temperature towards lethal levels (from 38 to 14° C.) gradually slows the heart rate and the atrioventricular conduction rate. After an initial rise during shivering (38 to 25° C.), the arterial pressure falls. The

electrocardiograms at reduced body temperatures show irregularities and, at still lower temperatures, atrioventricular block or obliteration of the P waves and nodal rhythms. The ventilation rate remains high relative to the oxygen uptake until body temperature reaches 21 to 17.5° C., when respiratory failure occurs. Above these latter temperatures, however, external respiration is adequate. Myocardial oxygenation remains adequate for the work performed at 20° C. if ventilation is controlled so as to maintain a normal arterial pH (Jude *et al.*, 1957).

Blood viscosity increases two- to three-fold between 39 and 20° C., principally because of hemoconcentration (hematocrit reading at 39° C. is 43.9 ± 8.62 , and at 20° C., 60.6 ± 5.60). Systole and isometric relaxation, and the Q-T interval of the electrocardiogram are prolonged progressively (6- to 7-fold increase at 18° C.), while the systole-to-cycle ratio tends to remain constant with cooling. Death is believed to be cardiac in origin and to be caused by inadequate coronary flow and diminished metabolic rate. These changes occur regardless of whether artificial pulmonary ventilation is given (Hegnauer *et al.*, 1950).

In experimental animals subjected to occlusion of venous inflow and right ventriculotomy during hypothermia, the right atrial pressure was elevated postoperatively which suggested myocardial failure. This could be prevented by administration of a rapid-acting digitalis preparation before occlusion of inflow or by perfusion of the coronary system with small volumes of oxygenated blood (Lombardo *et al.*, 1957).

TOXIC EFFECTS OF DRUGS

Digitalis. *Cardiovascular effects of digitalis.* Administration of digitalis to the patient with heart failure improves the circulation by increasing the cardiac output and the velocity of circulation (Moxitt, 1946). These in turn lead to salt-and-water diuresis, reduction of blood volume and systemic venous pressure, and relief of dyspnea, edema and other symptoms.

Tepper (1950) noted the effects of intravenous injection of strophanthin. In patients without heart failure, no significant changes were ob-

served. Both in patients with right heart failure and in those with left heart failure, the pulse rate and the arterial diastolic pressure declined. In those with left heart failure, the systemic venous pressure increased markedly and respiration became slower and deeper. In those with right heart failure, the systemic venous pressure fell an average of 5 cm. of water.

Effects of digitalis on the myocardium. This group of drugs acts primarily by increasing the functional capacity of the heart (Bloomfield *et al.*, 1950) through improved myocardial contractility. The improved contractility is manifested by ability of the myocardium to do a greater amount of work at a given initial length or, conversely, by its ability to assume a shorter initial length if the work remains unchanged. The improved cardiac action also results from greater and more prolonged systolic shortening and, at the same time, more complete filling of the ventricles in diastole (Walton, 1958). The effects of digitalis are not seen in the normal myocardium but become evident in failing muscle. For a detailed discussion of the effects of the cardiac glycosides on the energy metabolism of the normal and the failing heart, see Wollenberger (1949).

Effects of digitalis on heart rate. Cardiac slowing produced by digitalis, particularly in the presence of atrial fibrillation, also aids in improving cardiac efficiency. Slowing of the heart rate by digitalis represents in part the effect of the drug on the chemoreceptors in the carotid body, which in turn reflexly induces vagal discharge that inhibits the sinoatrial node and prolongs the refractory period of the atrioventricular node. This effect is blocked by atropine. The drug also directly affects the sinoatrial node to cause slowing of impulse initiation and directly prolongs the refractory period of the atrioventricular node, since atropine does not prevent cardiac slowing with larger doses of digitalis. This mechanism is particularly important in slowing the ventricular rate during atrial fibrillation (Movitt, 1946). However, the rise in cardiac output when Digoxin is given in heart failure is apparently as pronounced in patients with normal rhythm as in those with atrial fibrilla-

tion, and is not correlated with either the initial heart rate or the degree of cardiac slowing produced by the drug (Kelly and Bayliss, 1949). Digitalis occasionally has an antifibrillatory effect which may be attributed to the increase in refractory period or to the relief of dilatation resulting from the inotropic effects of the drug (DiPalma and Schultz, 1950). The drug appears to have no effect on the coronary vessels (Bing *et al.*, 1950).

Effects of toxic doses of digitalis. In toxic doses, digitalis tends to cause anorexia, nausea, vomiting, diarrhea, abdominal discomfort and restlessness, blurred, yellow vision, mental confusion, disorientation and psychosis. The heart may show abnormally prolonged atrioventricular conduction (more than 0.2 second), dropped beats and even complete atrioventricular block, premature beats, particularly of ventricular origin, bigeminal or trigeminal rhythm, atrial, nodal or ventricular tachycardias, or atrial or ventricular fibrillation. The appearance of any of these should be taken as an indication for stopping the administration of the drug (Movitt, 1946; Burwell and Hendrix, 1950). Digitalis in toxic doses may lead to increasing severity of heart failure, possibly by decreasing the myocardial efficiency (Batterman and Gutner, 1950).

Question of additive toxic effects of calcium and digitalis. Since calcium and digitalis have similar effects on the heart, it has been postulated that administration of calcium may potentiate the toxic effects of digitalis and *vice versa*. Administration of calcium chloride intravenously to digitalized dogs has led to death by ventricular arrest or ventricular fibrillation. However, it was found that the amount of calcium required and the blood levels reached were only slightly less than when calcium was administered alone (the differences being statistically insignificant), and that the electrocardiographic changes were identical with those of calcium poisoning (Hoff *et al.*, 1939; Friedman and Bine, 1948).

Digitalis and potassium. In tests on the embryonic duck heart, Friedman and Bine (1947) noted that absence of potassium led to arrhythmias and early cessation of beating; also that absence of potassium accentuated

ated the effects of Lantoside C but that excess of potassium inhibited the action of the Lantoside. They concluded that, while excess of potassium itself depresses the irritability of the heart, it may serve as a source of potassium to a heart which is losing potassium after exposure to toxic amounts of digitalis.

Digitalis in hyperthyroidism. In experimental animals with moderate hyperthyroidism, the administration of normal doses, and especially of toxic doses, of digitalis led to death, frequently with extensive degeneration or necrosis of myocardial fibers. In 3 animals, premature beats, paroxysmal atrial and ventricular tachycardias, ventricular fibrillation, changes in the diastolic base line, and decrease in amplitude or inversion of T waves were noted (Dearing *et al.*, 1950).

Quinidine. This drug is useful in changing atrial fibrillation to a normal rhythm and in decreasing the incidence of ventricular premature beats and fibrillation. It acts by prolonging the refractory period and slowing the rate of conduction (DiPalma and Schultz, 1950). In toxic doses, quinidine causes anorexia, mild nausea, vomiting, headache, drowsiness and tinnitus, syncope, peripheral vascular collapse, pulmonary embolism, delirium, temporary asystole, partial atrioventricular block, prolongation of the Q-T interval and slight notching of the T wave, and may even lead to ventricular fibrillation (DiPalma, 1958).

Quinine. Monkeys with a severe anemia resulting from malaria caused by *Plasmodium knowlesi* succumbed to smaller doses of quinine, given intravenously, than did normal monkeys or those with a mild degree of anemia. The malaria itself caused minimal changes (Ruskin and Rigdon, 1949).

Nicotinic Acid. Nicotinic acid had no effect on "normal" myocardium of isolated perfused hearts. In "failing" hearts, however, this substance caused a marked increase in amplitude of contraction and a reversal of abnormal rhythms (Calder, 1947).

Emetine. Patients receiving therapeutic doses of emetine experience weakness and marked decrease in tolerance to exercise but no change in blood pressure or heart rate.

The changes begin to appear about the eighth day and disappear during the first to fourth week after discontinuing the drug (Charters, 1950).

Procaine. Procaine has been administered intravenously for reducing cardiac irregularities and for relief of certain peripheral vascular disorders. In dogs, 4 to 80 mg./Kg. increased the width of the QRS complexes, prolonged the P-Q intervals, and caused ventricular tachycardia and ventricular fibrillation. All except the last changes were reversible if the dogs were given artificial respiration (Long *et al.*, 1949; DiPalma and Schultz, 1950).

Mercurial Diuretics. In the perfused isolated rabbit heart, Mercurhydrin* caused prolonged atrioventricular and intraventricular conduction, prolonged electrical systole, dropped beats and cardiac asystole. Thimerin Sodium* caused transitory ventricular ectopic beats and fibrillation and, in large doses, cardiac dilatation and decreased contractility and shift of the diastolic base line. Premedication with BAL (British anti-lewisite), ascorbic acid or thiamine tended to elevate the toxic levels of mercurials. These substances were, however, much less effective when given after signs of toxicity had developed (Ruskin and Johnson, 1949).

EFFECTS OF SMOKING

In normal medical students, smoking causes strikingly different patterns of response in different individuals, but the persons can be grouped to some extent. Those who have one parent, and especially those who have both parents with hypertension, have larger control cardiac outputs, and show greater increases (+14 per cent) in cardiac output than do those with non-hypertensive parents (+2 per cent). In general, these persons also have a greater increase of systolic pressure and heart rate, but not pulse pressure or stroke volume, than do persons without a family history of hypertension. Coronary disease in the

* Mercurhydrin is manufactured by Lakeside Laboratories, Inc., Milwaukee, Wisconsin; Thimerin Sodium, by Campbell Pharmaceutical Co., New York, N. Y.

parents is not associated with any augmentation of the responses (Thomas *et al.*, 1956).

Catheterization studies reveal that cigarette smoking in patients without heart disease results in a significant rise in coronary blood flow and heart rate and a significant decline in coronary vascular resistance and in the myocardial extraction of oxygen and glucose. No evidence of coronary vasoconstriction was noted (Bargeron *et al.*, 1957).

Injectations into a coronary artery of 0.05 μ g. of nicotine per Kg. of body weight cause a small decrease in cardiac contractility in anesthetized

dogs; injections of 0.25 μ g. per Kg. of body weight increase coronary flow and myocardial contractility. The latter effects are similar to those elicited by injections into a coronary artery of epinephrine or arterenol and are completely blocked by injections of 0.1 mg. of tetraethylammonium per Kg. of body weight. Injections of 0.5 mg. of nicotine per Kg. of weight elicit the coronary chemoreflex and decrease coronary flow. These effects are abolished by bilateral vagotomy. All of the above are believed to be a result of the nicotine upon sympathetic and parasympathetic ganglia in the heart (West *et al.*, 1956).

5. HEART FAILURE

Associated Circulatory Conditions

RELATION OF MYOCARDIAL WORK LOAD TO HEART FAILURE

Heart failure may best be defined as the inability of the myocardium to meet the circulatory demands placed upon the heart. The circulatory demand, which may be expressed as myocardial work, is the minute output of a ventricle multiplied by the mean pressure which the myocardium must develop within the ventricle to eject this quantity of blood. Increased pressure of ejection may be required either because of elevation of pressure in the arterial circuit or by narrowing of the orifice through which the blood must pass upon leaving the ventricle. Increased volumes of blood must be ejected in various conditions in which the demands by the tissues for blood is increased and also whenever valvular or septal defects are present which allow regurgitation of the ejected blood (Table V-2). Whenever the volume of blood to be ejected or the pressure required exceeds the capacity of either ventricle, heart failure ensues.

RELATION OF MYOCARDIAL EFFICIENCY TO HEART FAILURE

In the absence of increased work demands, the heart may fail if the amount of energy which may be developed by the contracting myocardium is impaired (Table IV-2).

Myocardial Weakness. According to Raab (1954), myocardial weakness is the principal

cause of congestive failure. He believes such weakness to be caused by the detrimental effect of exaggerated adrenosympathogenic catecholamine action on the myocardial oxidative energy economy. Acting jointly with the above is the influence of adrenal mineralocorticoids on myocardial electrolyte balance (increase of intracellular Na^+ and decrease of K^+). He believes that digitalis exerts its beneficial influence by correcting the effects of cardiac metabolism in both types of overactivity.

Limitations for Myocardial Work in Non-hypertrophied Heart with Normal Blood Supply. In the nonhypertrophied heart with a normal coronary circulation, the limits in the work output of the heart are probably determined by the mass of muscle and the amount of energy which can be developed by this mass. Angina, indicative of relative myocardial ischemia or anoxia, is not seen.

Limitations Imposed by the Coronary Circulation. Limitation of production of energy by the myocardium may also be caused by inadequate blood supply in coronary insufficiency, i.e., by narrowing without complete occlusion of the coronary vessels (Bing *et al.*, 1949) and in various forms of anoxia: (a) respiratory anoxias, including cyanotic types of congenital heart disease in which the blood is insufficiently oxygenated; (b) anemic anoxia, such as is seen with decreased concentration of hemoglobin or red cells and in carbon monoxide poisoning; (c) stagnant anoxia, such as

TABLE V-2

Factors Causing or Contributing to Heart Failure

I Mechanical overloading of heart

A. Increased resistance to ejection of blood by left ventricle

- 1 Stenosis of orifice of aortic valve or lumen of aorta
- 2 Coarctation of aorta
- 3 Systemic arterial hypertension (elevation of mean arterial pressure)
- 4 Adhesions between ventricle and chest wall

B. Increased resistance to ejection of blood by right ventricle

- 1 Stenosis of orifice of pulmonary trunk (tetralogy of Fallot)
- 2 Pulmonary hypertension resulting from
 - a. Pulmonary arteriolar sclerosis
 - b. Pulmonary emphysema
 - c. Mitral stenosis
 - d. Left ventricular failure
 - e. Patent ductus arteriosus or persistent truncus arteriosus

C. Excessive demand for output affecting left ventricle only

- 1 Aortic insufficiency
- 2 Mitral insufficiency
- 3 Patent ductus arteriosus

D. Excessive demand for output affecting right ventricle mainly

- 1 Patent septal defects, particularly of atria
- 2 Eisenmenger complex (ventricular septal defect with dextroposition of aorta)

E Excessive demands for output affecting both ventricles

- 1 Arteriovenous fistula

2. Excessive exercise

3 Hyperthyroidism

4 Anemia

5. Anoxia (all types)

6. Excessive blood volume (as after transfusion, infusion, and overdosage with desoxycorticosterone)

7. Fever (artificial or accompanying infections)

8. Coughing

9 Digestion of large meals

10 Pregnancy

11. Ventricular septal defect

II. Primary myocardial insufficiency

A. Loss of myocardial fibers

1. Myocardial infarction

2 Diffuse myocardial fibrosis

B. Impaired myocardial circulation

1 Coronary insufficiency

a. Narrowing of coronary vessels

b Excessive myocardial hypertrophy

2. Excessive tachycardia

3 Anoxia

a. Respiratory

b. Anemic

c Stagnant

d. Tissue

4. Aortic stenosis or insufficiency

C. Impaired myocardial contractility

1 Myxedema

2. Thiamine deficiency

3. Myocarditis

III Impaired cardiac filling

A. Excessive tachycardia or cardiac irregularities

B. Adhesive pericarditis

C. Cardiac tamponade

is seen after prolonged arterial hypotension; and (d) tissue anoxia, such as seen with cyanide poisoning. The third may be seen after injection of excessive quantities of the coronary constrictor agent, pitressin. The last may develop as a result of administration of epinephrine, since this substance may increase the oxygen consumption more than it increases the work output of the myocardium. Reduction in work output of the myocardium, of course, also results from necrosis of myocardial tissue following coronary occlusion. Excessive increase in right ventricular pressure may seriously limit right coronary blood flow, leading to right ventricular failure. In the presence of myocardial hypertrophy, cardiac work is usually increased at rest, but the hypertrophy is not accompanied by a corresponding increase in the blood supply. As a consequence, the maximum increase in the

work of such hypertrophied heart during exertion will be less than that of the normal heart. In myxedema and thiamine deficiency and probably in the various forms of acute myocarditis, the decrease in the ability of the myocardium to meet the work demands is probably caused by a decrease in the amount of energy which can be developed per gram of myocardium (Katz, 1940). The myofibrils may be physicochemically altered, leading to inefficient utilization of the energy for contraction; improvement with digitalis may be caused by an action on the mitochondria, the presumed site of energy production in the myocardial fibril (Leiter, 1957).

Extra-cardiac Factors Limiting Myocardial Work. Reduction in development of energy and ejection of blood by the heart may result from cardiac tamponade or from constrictive pericarditis, both of which interfere with fill-

ing of the ventricles and may produce symptoms similar to heart failure.

RESPONSE OF MYOCARDIUM TO INCREASED WORK LOAD

Starling's Law of the Heart. Increase in the initial length of the ventricular muscle fibers increases the energy released during the ensuing systole. The increased length is brought about by augmenting the volume of blood in the ventricle at the end of diastole, and is accompanied by an increase in the initial tension, *i.e.*, by an increase in the pressure in both the ventricle and the atrium at the end of diastole. The extra energy may be used by the ventricle to eject a larger volume of blood against the same arterial pressure, to eject the same volume of blood against a higher arterial pressure, or to do both. If, however, the distention of the ventricle exceeds a critical limit, its ability to eject blood begins to decrease progressively with further increase in diastolic size; the heart is then in a stage of decompensation or acute failure (McMichael, 1950). The normal heart, however, often does not increase in size with moderate increase in work, and may even decrease in size (Richards, 1949).

FACTORS LEADING TO INCREASED DIASTOLIC VOLUME OF VENTRICLE

Increased Venous Return. An increased atrial pressure may be brought about by transfusions, by mobilization of blood from blood reservoirs such as the liver and spleen, by expressing blood from the muscle during exercise, or by the occurrence of shunts or arteriolar dilatation. In addition, acute increase in venous return in edematous patients may occur at night because of resorption of the edema fluid. As a result of the increased diastolic filling, the normal ventricle is enabled, within limits, to eject larger volumes of blood per beat. Increased left ventricular diastolic size is also brought about by regurgitation through an insufficient aortic valve; and increased right ventricular initial length, by atrial and ventricular septal defects.

Increased Resistance to Ejection. When the work load is increased by elevation of the

arterial pressure, the heart, for a few beats, fails to eject as much blood as it had previously. This leaves a residuum in the ventricle which, combined with the normal return during the next few diastoles again increases the initial length, and therefore the energy, which can be released by the ventricle during the ensuing systole. As a consequence, the ventricle is then enabled to eject the normal amount against the higher arterial pressure.

EFFECT OF CHRONIC INCREASE IN DIASTOLIC VENTRICULAR VOLUME

Increase either of venous return or of arterial resistance leads to dilatation of the ventricles. Such dilatation disappears immediately if the work load is reduced but with persistence of increased work load, such as is seen with valvular defects, the dilatation is maintained. After a period of days to weeks, the dilatation leads to hypertrophy of the muscle fiber, thus increasing the work which can be done during a given systole and resulting in return of the initial ventricular volumes toward normal but, of course, never completely back to normal. The hypertrophy may eventually disappear if the work load is returned to normal but if the increased work load persists indefinitely, the hypertrophy is likewise maintained (Hall *et al.*, 1953). Further augmentation in work load, as by additional damage to the valve, leads to further dilatation followed by increased hypertrophy. Eventually, if the work load is progressively increased, a stage is reached in which the muscle mass has increased out of proportion to the coronary blood supply. Further increase in the work demands of the heart then cannot be met, owing to inability of the coronary vessels to supply sufficient blood, and leads to chronic failure (Shipley *et al.*, 1937).

MYOCARDIAL METABOLISM

Patients with heart failure resulting from valvular heart disease, have a decreased oxygen saturation of the coronary venous blood and an increased arteriovenous oxygen difference in concentration which appears to be correlated with the magnitude of ventricular

dilatation. The blood flow and oxygen consumption per 100 grams of left ventricle are within normal limits. These patients have no defect in production of aerobic oxidative energy but fail to convert oxidative energy into effective mechanical work (Coodale *et al.*, 1950).

FUNCTIONAL DISTURBANCES IN ACUTE HEART FAILURE

The phenomena accompanying failure of the heart may be divided according to whether they occur with acute failure or with chronic failure. To some extent they are similar and overlap. Acute heart failure, in many respects, resembles traumatic or hemorrhagic hypotension and shock. Acute heart failure may be initiated by phenomena, such as sudden onset of extreme tachycardia, myocardial injury resulting from coronary occlusion, or cardiac tamponade caused by rupture or a stab wound of a vessel. It may also be precipitated in a patient with mild chronic heart disease by strenuous physical activity; by minor respiratory infections, particularly if cough is present; abruptly with onset of tachycardia; or following absorption of dependent edema on retiring (nocturnal dyspnea, "cardiac asthma") (Orgain and Stead, 1957).

Symptomatology. Symptoms and signs include weakness, faintness, diminished mental alertness, pallor, cold moist skin, feeble, thready, rapid pulse and diminution of blood pressure and, in coronary occlusion, persistent anginal pain. In addition, dyspnea, orthopnea and pulmonary edema may be present, and peripheral veins may be normal, distended or collapsed.

In experimental animals, the left ventricle and pulmonary circulation were found to contain 13 per cent of the blood volume. Acute left heart failure, produced by partial constriction of the ascending aorta, led to a 70 per cent increase in the volume of blood in these structures; acute right heart failure, produced by partial constriction of the pulmonary artery, led to a 48 per cent decrease (Lindsey *et al.*, 1957).

Cardiac Output. Measurements of cardiac

output in acute heart failure are not available in any quantity, probably because of the poor condition of the patient. However, the current consensus seems to be that the output is reduced below normal for the patient. As a consequence of the reduced stroke volume output by the heart, the pulse pressure becomes narrow and the pulse thready. The lowered arterial pressure causes reduced cerebral blood flow, resulting in weakness, faintness and diminished mental awareness.

Pulmonary Edema. A large infarct, involving principally the left ventricle, causes a sudden reduction of output of the left ventricle with respect to the output of the right ventricle. This leads, therefore, to a progressive increase in pressure in the left atrium and ultimately in the pulmonary capillaries, with increase in the filtration pressure and occurrence of pulmonary edema and orthopnea. The degree of pulmonary edema probably depends on whether chronic congestive heart failure has been present prior to the onset of the acute coronary occlusion.

Venous Pressure. Peripheral venous distention may not be marked in the absence of an increase in blood volume; in fact, the peripheral veins may actually be collapsed, possibly because of venous constriction in response to the decreased minute volume of circulation.

FUNCTIONAL DISTURBANCES IN CHRONIC CONGESTIVE HEART FAILURE

Symptomatology. Chronic heart failure (Table V-2) is characterized by a gradual onset with repeated attacks of mild heart failure with exertion, gradually progressing to heart failure, even at rest, if the cardiac lesion becomes severe enough. Symptoms and signs which may result from chronic heart failure include dyspnea on exertion and, if severe, even dyspnea at rest, venous distention, edema, ascites, hydrothorax, enlargement of the liver, cyanosis, pulmonary edema, cough, tachycardia, cardiac enlargement, cachexia, fatigue and albuminuria.

Severity of Chronic Heart Failure. Heart failure may be graded as mild, moderate or severe. The classifications here given are

slightly modified from those of the New York Heart Association (1953, page 81).

Class I. No heart failure (cardiac disease without limitation of physical activity). In this class are placed persons with cardiac disease, if ordinary physical activity does not produce symptoms referable to the heart.

Class II. Mild heart failure (cardiac disease resulting in slight limitation of physical activity). At rest, symptoms are absent, cardiac output is normal, and the ratio of tissue oxygen supply to metabolic demand is normal. Ordinary physical activity may result in fatigue, palpitation, dyspnea or anginal pain, and the oxygen index is slightly below normal. With severe exertion, cardiac output fails to increase in proportion to the exertion, marked dyspnea is induced, and there is a considerable increase in arteriovenous oxygen difference and reduction in the oxygen index.

Class III. Moderate heart failure (cardiac disease resulting in marked limitation of physical activity). Less than ordinary activity causes fatigue, palpitation, dyspnea or anginal pain. No symptoms are noted at rest but the cardiac output is slightly decreased below normal, with a resulting slight increase in arteriovenous oxygen difference and reduction in the oxygen index. With moderate exertion, the cardiac output fails to increase adequately, causing severe dyspnea, a considerable increase in the arteriovenous oxygen difference, and a marked reduction in the oxygen index.

Class IV. Severe heart failure (cardiac disease resulting in inability to carry on any physical activity without discomfort). Even at rest, symptoms of cardiac insufficiency or of the anginal syndrome may be present. The cardiac output and oxygen index may be reduced considerably and the arteriovenous oxygen difference increased. Discomfort is increased by any physical effort. Very little increase in cardiac output occurs with moderate exertion or such exertion may even lead to a reduction in cardiac output, marked increase in arteriovenous oxygen difference and reduction in the oxygen index.

Right vs. Left Heart Failure. *Impairment of right ventricular function.* Primary chronic right-sided heart failure (cor pulmonale) usually results from parenchymatous disease of the lung or obstruction of pulmonary blood flow, it may result from primary pulmonary hypertension or repeated small pulmonary emboli. Such failure is characterized by dyspnea, cyanosis, polycythemia, clubbing of the fingers and toes, elevation of systemic venous pressure, enlargement of the liver and systemic edema.

Experimental studies in animals indicate that, in the absence of pulmonary arterial hypertension or stenosis, it is possible to maintain circulation in the face of severely impaired right ventricular function *per se*. However, this usually requires an increase of blood volume and associated elevation of venous pressure, ascites and peripheral edema. Pulmonary congestion will be absent (Boucek *et al.*, 1952; Donald and Essex, 1954; Rose *et al.*, 1956).

Impairment of left ventricular function. Experimental pure left-sided failure may be produced by sudden opening of a shunt between the subclavian artery and the left atrium in dogs. Such failure causes acute left ventricular dilatation and fibrillation, a rise in left atrial pressure, and congestion and edema of the lung, and occasionally hypertrophy of the media of the small muscular arteries of the pulmonary bed and thickening of the intima of the pulmonary arterioles but does not lead readily to increase of blood volume or to systemic congestion (Boucek *et al.*, 1952; Rodbard *et al.*, 1956).

Cardiac Output. No absolute level of cardiac output is necessarily associated with heart failure. In otherwise normal patients with a disturbance limited to the myocardium, such as a myocardial infarction, or with a stenotic valvular defect, there may be mild cardiac failure. The cardiac output at rest may be within normal limits but, with exertion, the cardiac output fails to increase to the extent that it would in normal persons. The more severe the cardiac failure, the less is the increase in output with exercise until, with dyspnea, cardiac output is reduced below

normal, even at rest (low-output failure). In some instances, heart failure may be present at rest with an output which would be regarded as normal or even above normal, but almost invariably these persons have an associated anemia, an elevated metabolic rate or a structural defect such as patent ductus arteriosus or arteriovenous fistula (high-output failure; Stead, 1949). In hypothyroidism (myxedema), on the other hand, the cardiac output may fall to low levels without the development of cardiac failure (Orgain and Stead, 1957).

Systemic Blood Flow. Concurrently with the decrease in cardiac output, systemic blood flow is reduced. Arterial pressure, however, is often not decreased. Normal arterial pressure is maintained as the result of peripheral systemic vasoconstriction which is probably induced reflexly.

The vasoconstriction is evident in the skin and kidneys. Cutaneous vasoconstriction may be, in part, responsible for the slight fever occasionally seen in patients with cardiac failure. Vasoconstriction in the kidney is usually quite intense in congestive heart failure and may diminish renal blood flow to as little as one-third of normal (Stead, 1948). The reduced renal flow is probably responsible in part for the retention of salt and water which contributes to the edema in heart failure. Cerebral blood flow was found by Scheinberg (1950) to decrease in proportion to the cardiac output in heart failure. Cerebral oxygen consumption was significantly reduced below normal, and the cerebral arteriovenous difference in oxygen concentration and the cerebral vascular resistance to flow both increased. The hepatic (splanchnic) blood flow in 13 patients with cardiac failure was found to be 200 to 800 (average 535) ml. per sq. M. of body surface. In 14 control persons the hepatic blood flow was 600 to 1160 (average 850) ml. per sq. M. of body surface. In the first group the difference in concentration of oxygen between artery and hepatic vein was 5.5 to 12.8 ml. O₂ per 100 ml. of blood, whereas in the controls the difference was 3.3 to 5.9 ml. O₂ per 100 ml. of blood.

The reduction in hepatic flow, in contrast to that in the kidney, was found to be roughly proportional to the simultaneous decrease in cardiac output (Myers and Hickam, 1948).

Oxygen Index. Perhaps the most constant finding in all types of heart failure is a disproportion between the cardiac output and the metabolic rate (Briggs *et al.*, 1948), *i.e.*, the ratio of the oxygen supplied by the blood to the tissues per minute, to the metabolic rate of oxygen taken up by the tissues per minute. Little (1949) called this ratio the oxygen index (O.I.). It may be expressed mathematically as follows:

$$\begin{aligned} \text{O.I.} &= \frac{\text{O}_2 \text{ supply/sq. M.}}{\text{O}_2 \text{ consumption/sq. M.}} \\ &= \frac{\text{Arterial O}_2 \text{ (ml./100 ml. blood)}}{\text{A-V O}_2 \text{ difference in ml./100 ml.}} \end{aligned}$$

Variations in oxygen index in heart failure.

The oxygen index is reduced at rest and is markedly reduced with exertion in many forms of heart failure, particularly congestive heart failure, the degree of reduction depends on the severity of the symptoms associated with the exertion. Hickam and Cargill (1948) plotted the arteriovenous oxygen difference against the oxygen uptake and found that, in normal persons, large increases in oxygen consumption with exercise are accompanied by only slight elevations in arteriovenous oxygen difference. In other words, the cardiac output parallels the metabolic demands of the tissues. In patients with congestive heart failure, however, exertion may be accompanied by a marked increase in the arteriovenous difference in level of oxygen. In such patients the cardiac output has failed to increase in proportion to the oxygen consumption. In patients with mitral stenosis without congestion, cardiac output and arteriovenous differences are normal at rest; however, in these patients also the cardiac output does not increase normally with exercise and, as a result, a much greater increase in arteriovenous difference is seen in these patients than in normal persons (low-output failure) (Hickam and Cargill, 1948).

Cardiac output does not increase with

anemia until the hemoglobin is reduced to around 7 grams per 100 ml. With hemoglobin below this level, cardiac output at rest progressively increases, but the oxygen supplied to the tissues is always proportionately less than the metabolic rate, with the result that the arteriovenous difference is always increased. A still further marked reduction in the ratio of oxygen supply to oxygen demand is observed with exertion, particularly in the presence of heart failure (high-output failure) (McMichael, 1947).

Pulmonary Edema. Pulmonary edema may be seen following exercise, sudden mechanical overload of an impaired left ventricle, in severe mitral stenosis or following sudden reduction of contractile myocardium by myocardial infarction, and in coronary insufficiency involving preponderantly the left ventricle; i.e., in any condition in which the left atrial pressure may be abnormally elevated, leading to elevation of pulmonary capillary pressure. The occurrence of edema depends, of course, upon a reasonably adequate functioning of the right ventricle which must develop sufficient pressure to raise the pulmonary capillary pressure above the oncotic pressure of the plasma proteins. In patients with moderate chronic heart failure with increase in blood volume and dependent edema, pulmonary edema is especially likely to develop upon retiring and to lead to the phenomenon of nocturnal dyspnea or cardiac "asthma." This is the result of mobilization into the blood of tissue fluid which was entrapped in the dependent portions while the patient was erect. This phenomenon may at times be precipitated by an exciting dream which presumably serves to mobilize extra blood from the blood reservoirs (Hilden, 1949, Orgain and Stead, 1957).

Pulmonary edema may be initiated also by irritating pulmonary poisons which change the permeability of the capillaries and by lowering the concentration of plasma proteins. As pulmonary congestion develops, the oxygen tension of the arterial blood begins to decline, but the oxygen concentration (saturation) is not appreciably affected because of the associated hyperventilation. However, if

ventilation is even slightly impaired, the oxygen concentration of the arterial blood may be markedly lowered (Orgain and Stead, 1957).

Therapy of pulmonary edema is most successful when utilizing morphine, mercurial diuretics and sympathetic blocking drugs, oxygen therapy, pressure respiration or venesection. Most of these tend to reduce venous return and cardiac output. They may be helpful in patients in whom the edema is associated with a full pulse and high blood pressure and cardiac output (group I) but they may induce shock in patients who have low cardiac output and arterial pressure (group II) (Luisada and Cardi, 1956).

Blood Velocity (Circulation Time). Evidence for increased pulmonary capillary pressure in mechanical overloading of the ventricle and in mitral stenosis is found in decreased velocity of blood flow through the lungs. This can be estimated from arm-to-tongue circulation time. Since the circulation time is prolonged relatively much more than the cardiac output is reduced, one must assume that the vascular system between the arm veins and the tongue, including principally the pulmonic capillary bed, is dilated and thereby leads to a more sluggish rate of flow.

Blood Volume. Most authors agree that blood volume is increased in chronic heart failure, particularly in the presence of systemic congestion (Perera, 1945). The increased blood volume closely parallels the increase in total weight of the body and the degree of edema (Funkhouser, 1957). An increase in the total number of circulating red cells (Guntton and Paul, 1955; Nylin, 1955) and an increase in the total number of grams of circulating protein are also seen in heart failure, but the concentration of protein and of red cells is less than normal.

Sodium Chloride and Water Excretion. Studies in congestive heart failure indicate a reduction in excretion of salt and water (Borst, 1948). Retention of sodium appears to be the primary factor for the following reasons: (a) Patients with congestive failure may be relieved of their edema without restriction of water intake, provided that either

sodium intake is restricted or diuretics, which increase sodium excretion, are administered, (b) if cardiac patients who have just recovered from edema are given sodium chloride, they rapidly reaccumulate edema; on the other hand, if they are given free access to water, edema does not increase and may even be reduced; (c) the effect of the sodium chloride seems to be related to the sodium ion since administration of sodium bicarbonate increases edema, whereas administration of ammonium chloride leads to a reduction of edema (Stead, 1948; Friedberg, 1957).

This reduction in sodium excretion may be brought about by at least two mechanisms

(a) A reduced glomerular filtration parallels the reduction in cardiac output. Sodium excretion decreases rapidly as glomerular filtration falls and ceases when the sodium load presented to the kidney falls below 3.9 millimoles per minute in each kidney. Thus, sodium excretion may be reduced relatively more than cardiac output, renal blood flow or glomerular filtration.

The decreased excretion of sodium does not appear to be related to diminution in any specific tubular function since the maximum tubular capacity for excretion of para-aminohippurate and for reabsorption of glucose are within normal limits; there is relatively little difficulty in excreting water, potassium or non-electrolytes; and the ability to excrete hydrogen ions and ammonia remains good (Grossman *et al.*, 1950, Orgain and Stead, 1957). The reduction in renal blood flow and the renal efferent arteriolar constriction in congestive failure do not appear to be the result of reflexes, they may be initiated by a humoral mechanism (Merrill *et al.*, 1946, Mokotoff and Ross, 1948, Selkurt *et al.*, 1949).

(b) In congestive heart failure 95 to 98 per cent of the filtered sodium (instead of the normal value of 90 to 95 per cent) is reabsorbed. This increased reabsorption may be more important than the reduction in glomerular filtration in explaining the retention of sodium in the body in congestive failure. There is some specific stimulus to the tubules to reabsorb sodium (Burch and Reaser, 1946; Merrill, 1949). This stimulus may be an increased rate of secretion of aldosterone (the electrolyte retaining hormone) by the adrenal cortex, since this hormone appears in greater concentration in the urine in heart failure. Adrenalectomy decreases the edema of heart failure, presumably without increasing glomerular filtration.

On the other hand, aldosterone-producing tumors do not cause edema in the absence of heart failure. Two mechanisms may therefore operate synergistically (Orgain and Stead, 1957). Hypophysectomy reduces but does not abolish the aldosterone secretion that occurs when cardiac output is reduced by thoracic inferior vena cava constriction. Therefore aldosterone secretion is not dependent solely on the hormone of the posterior pituitary (Davis *et al.*, 1957).

Water is also retained with the sodium, probably in an attempt by the body to maintain osmotic equilibrium rather than a direct effect from the mechanism leading to the sodium reabsorption. Increased secretion of Pitressin by the pituitary body may be responsible for retention of water which accompanies salt retention. An antidiuretic factor has been extracted from the urine of patients with congestive failure; however, it does not have the characteristics of commercial Pitressin (Bercu *et al.*, 1950).

Impairment of liver function may be related to production of edema in chronic congestive failure, which in turn may be the result of inability of the liver to inactivate an antidiuretic factor (Zak, 1949). In line with this hypothesis, is the observation that diuretic therapy is more effective in the presence of a normal liver (as determined by biopsy of tissue removed by needle) than when the liver shows evidence of cirrhosis (White *et al.*, 1951).

Elevation in Central Venous Pressure. Common accompaniments of cardiac failure are a rise in the central venous pressure and distention of the central systemic veins. Three mechanisms could be responsible: (a) acute failure of the right ventricle to remove blood from the central venous reservoir at the same rate that blood is returning from the periphery. This mechanism would be comparable to that leading to a rise in left atrial and pulmonary capillary pressure seen in acute failure of the left ventricle; (b) an increase in total blood volume with resulting distention of all the blood vascular system. Since the central venous reservoir is the most distensible, this might be expected to contain the greatest quantity of added blood volume; and (c) a

reduction in vascular capacity (venous constriction). It is probable that all three mechanisms play a part.

Role of Impaired Cardiac Ejection. With exercise, the central venous pressure rises slightly in normal persons and markedly in patients with cardiac disease. In both, the rise may be caused by increased venous return. However, in patients with cardiac disease, the increased return may cause such an increase in the diastolic volume of the heart that the heart decompensates, with the result that the cardiac output per beat is reduced by the overdistension. This would lead to further retention of blood in the ventricle (Nylin, 1955) and to a rise in the central venous pressure.

Role of Blood Volume. Venous pressure rises only late in congestive failure, after a considerable increase in blood volume has occurred, and returns towards normal before the blood volume is restored to normal. Furthermore, the venous pressure after death in persons who die of congestive heart failure is much higher than in those who die from other causes (Starr, 1940). The increase in blood volume appears, therefore, to be a cause of the rise in central venous pressure rather than the reverse.

Role of Reduction of Vascular Capacity. In heart failure from anemia, the blood volume is below normal and the cardiac output is above normal both at rest and during exertion, but the central venous pressure, while normal at rest, becomes elevated with failure. This can be explained only by a reduction in vascular capacity during rest, with further reduction during exercise. The reduction of vascular capacity, i.e., venous constriction, must depend on some humoral mechanism for its genesis (McMichael, 1949). As compared to normal controls, decreased distensibility of the venous bed of the forearm, interpreted as indicating peripheral venoconstriction, is noted in patients with heart failure regardless of whether the peripheral venous pressure is elevated (Wood et al., 1956).

Parallelism of venous pressure and venous oxygen tension. Little (1949) made a statis-

tical study of the relationship between the central venous pressure and various other measures of cardiac function. He found that, while venous pressure tended to become progressively elevated with increase in blood volume, the correlation was not good. A much better correlation was found between the increase in venous pressure and the venous oxygen partial pressure. He postulated that a reduction in the venous oxygen partial pressure in some way stimulates the mechanism leading to a reduction in vascular capacity, which in turn expresses the blood toward the central venous reservoir. He stated that the operation of this mechanism explains, in part at least, the rise in central venous pressure seen in normal persons with exercise and the much greater rise seen in patients with heart failure, since in the latter the venous oxygen partial pressure is reduced much more.

Possible relationship to blood lactic acid. In order to accept the venous oxygen partial pressure as the stimulus for such venous constriction, it will be necessary to find in the systemic venous or the pulmonary arterial circuits, chemoreceptors capable of sensing the venous oxygen partial pressure. Since no such mechanism has as yet been described, it seems possible that the stimulus to reduction of vascular capacity might arise from the chemoreceptors known to exist in the systemic arterial circuit. In severe exertion or in other conditions in which the oxygen supply to the tissues is reduced below normal, i.e., in which the arteriovenous oxygen difference is increased or the venous oxygen partial pressure reduced, lactic acid and other abnormal products of metabolism are produced. Since these products are not removed by the lungs, it might be anticipated that they could be carried to the systemic arterial circuit where they could excite appropriate chemoreceptors in the aortic and carotid bodies. Supporting this point of view is the prolongation of the rise in venous pressure and cardiac output seen during the period of oxygen debt following exertion, during which it has been shown that lactic acid remains elevated in the circulation.

Arterial and venous constrictor mechanisms.

Discharge of impulses from the chemoreceptors will induce increased sympathetic nerve discharges from the medullary centers. This will cause widespread increase in peripheral resistance by causing arteriolar and terminal arterial vasoconstriction. This must be the mechanism for maintaining the arterial pressure at normal levels despite the decreased cardiac output (Stewart *et al.*, 1946). This mechanism is possibly overactive during heart failure, since the mean arterial pressure of many patients declines as compensation returns. Such sympathetic activity could also serve to reduce the capacity of the vascular bed by causing afferent arteriolar constriction and efferent venular dilatation in the spleen, liver and intestines and generalized constriction of the larger veins. The increased sympathetic nerve activity could also serve to increase the contractile power of the heart and thus to increase the cardiac output at least in normal persons. An example of the operation of such a mechanism is the response to intravenous injection of epinephrine. This not only increases the arterial pressure, but also causes a rise in central venous pressure, a reduction in splenic volume and an increase in cardiac output. It is also possible that, to some extent, the increased cardiac contractility might be produced by the direct effect of metabolic products in the blood, particularly lactic acid, acting upon the myocardium.

Systemic Edema. The increase in tissue fluid and the systemic edema of congestive failure are closely correlated with the gain in body weight. They are not due solely to the elevation of central venous pressure or to a reduction in total plasma proteins and tissue tension since: (a) In congestive heart failure, the total circulating proteins are increased despite the reduction in concentration of protein, and (b) the elevation in venous pressure in the dependent part of the body caused by the rise in central venous pressure is rarely more than 10 to 15 cm. of water, whereas in the normal person, standing quietly, the pressure in the veins in the feet is of the order of 100 cm. of water. However, the venous hydrostatic pressure is a major factor in determining the distribution of the edema, since it

always occurs in the most dependent parts of the body (Orgain and Stead, 1957). The edema of congestive failure does not result from increased capillary permeability to protein (Stead and Warren, 1944).

More important in the development of edema is the retention of sodium and water by the kidney. This will serve to elevate blood volume and capillary pressure and to reduce the effective oncotic pressure of the plasma proteins to the point where filtration of water and dissolved substances into the tissues must occur, thus leading to edema.

Pleural effusion is a frequent finding in chronic congestive failure. In one series of 42 patients, the effusion was on the right side in 28 and was bilateral in one. The exact mechanism of production of the effusion is not known. Both increased intracapillary pressure and increased capillary permeability are involved (Tinney and Olsen, 1945).

Hepatic congestion. Swelling and tenderness of the liver are seen frequently with heart failure. Most of the cellular damage and congestion is in the region of the central veins. The changes have been ascribed to the mechanical effect of the elevated systemic venous pressure. However, the pressure in the periphery of the lobules, where the blood from the portal vein enters the hepatic capillaries must be higher than that in the capillaries near the central veins of the lobules from which the blood leaves the lobule to enter the hepatic vein. Such damage, on the other hand, could result from hypoxia owing to decreased blood flow; the hepatic cells in the periphery of the lobules, being the first to receive the portal venous blood, would be better oxygenated than the hepatic cells located in the center of the lobules. The occurrence of similar lesions in the liver in anemia favors this latter concept. Liver function may be disturbed in heart failure. Serum bilirubin is frequently elevated, the proportion of the slow-reacting (indirect) component being increased (Schalm and Hoogenboom, 1952); and there may be retention of bromsulfalein (Paine and Smith, 1919).

Hyperpnea, Dyspnea and Orthopnea. Hyperpnea is a clinical sign and may be de-

finer as increased minute-volume of breathing, the rate or depth of breathing, or both, being augmented. Dyspnea is a clinical *symptom*, noted by the patient, of difficult or labored breathing or of unsatisfied desire for air. While the two frequently occur together, there is no close parallelism in their intensity, and moderate hyperpnea may occur in the normal person without dyspnea.

Chemical Factors Contributing to Hyperpnea. *Hypercapnia.* Although the function of respiration would seem to be proper oxygenation of arterial blood, ordinarily the medullary respiratory center is principally concerned with regulation of arterial blood pH through its control of elimination of carbonic acid. A very slight increase in arterial $p\text{CO}_2$ of $+1.5$ mm. Hg (normal 40 mm. Hg) or decrease in pH, by their effect on the medullary center, results in doubling of the respiratory minute volume. Respiration is slowed in a similar manner by reduction of $p\text{CO}_2$. With excessive elevation of arterial $p\text{CO}_2$, additional reflex stimulation of the medullary respiratory center occurs through impulses generated in the carotid and aortic body chemoreceptors and transmitted to the medullary centers by way of the ninth and tenth cranial nerves.

Hypoxia. An increase in $p\text{O}_2$ above normal has no effect on the respiratory minute-volume; and a considerable decrease in arterial $p\text{O}_2$ (from 100 to 70 mm. Hg) is necessary to double the respiratory minute-volume, through its influence on the carotid and aortic bodies. The relatively high percentage of oxygen in the inspired air (20.9 per cent) compared with the lower percentage of CO_2 in the alveolar air (5.5 per cent) assures a sufficient respiratory exchange which will eliminate the proper volume of CO_2 and cause an intake of a slightly larger volume of oxygen than is required under normal circumstances (respiratory quotient = volume of CO_2 eliminated per volume of O_2 consumed = 0.8).

* $p\text{CO}_2$ is the "partial" pressure of the CO_2 , i.e., the pressure which it is constantly exerting to escape from solution or to diffuse through membranes. The term $p\text{O}_2$ used below refers similarly to the "partial" gas pressure exerted. The term "partial" refers to that part of the total gas pressure which is exerted by the indicated gas.

Lactic acid and other metabolites. Lactic acid and possibly other products accumulate in the blood whenever tissue oxygenation is incomplete, and serve as potent stimulants to respiration. Lactic acid may affect both the medullary centers and the carotid and aortic body chemoreceptors; the former are probably the more sensitive.

Relationship of Heart Failure to Hyperpnea. *Reduced minute-volume of circulation.* Reduction of the minute-volume of circulation will decrease the delivery of oxygen to the tissues, increase the oxygen utilization (ml. of oxygen removed per 100 ml. of blood flowing through the tissues) and lower the average oxygen tension in the tissue capillaries. At a critical level, lactic acid will be produced which will serve to stimulate respiration, probably simultaneously with activation of the arterial and venous constrictor mechanisms. Under such circumstances, arterial $p\text{O}_2$ will be normal and the $p\text{CO}_2$ may be reduced below normal.

Pulmonary congestion and edema. Exchange of pulmonary oxygen and carbon dioxide is reduced in the presence of relative failure of the left ventricle by the thickening of alveolar walls and alveolar accumulation of fluid. As a consequence, arterial $p\text{O}_2$ declines and $p\text{CO}_2$ rises. These changes, added to the accumulation of lactic acid noted above, provide further stimulus to hyperpnea during episodes of heart failure (Platts, 1953).

Dyspnea. Since dyspnea is a sensation, its elucidation is limited to studies on man. Wiggers (1949) has proposed that dyspnea be regarded as present when the expiratory muscles are brought into play; but, in the absence of an adequate statistical comparison of the severity of symptoms with the degree of use of the expiratory muscles, it is probably better to continue to define dyspnea as given above. The term "active expiration" might be more suitable for the sign defined by Wiggers as dyspnea.

A form of dyspnea, characterized by shortness of breath or air-hunger, is probably caused by failure of the cardio-respiratory machinery to prevent undue changes in concentration of arterial $p\text{O}_2$, $p\text{CO}_2$, or lactic

acid. Actual labored or difficult breathing, which is sometimes characterized as a sense of constriction of the chest, occurs in asthma and emphysema and is probably related to mechanical difficulty in movement of the tidal air. Similar difficulty may be experienced with excessive elevation of the diaphragm by abdominal distention and with the impaired elasticity of the congested lung in heart failure.

Cardiac failure is frequently attended by a decrease of vital capacity and of residual air. Because of the associated changes in lung compliance, airway resistance, and non-elastic tissue resistance, it requires more effort to move air in and out of the rigid lungs and, with an impaired blood supply, the muscles of respiration become fatigued (Comroe, 1956, Orgain and Stead, 1957). However, other "neurologic" factors may need to be considered since dyspnea may be experienced by persons even when their respiratory muscles are doing little or no work, as in patients with poliomyelitis who have involvement of the respiratory muscles, and in persons who have been given curare to the point of developing paralysis of the respiratory muscles (Comroe, 1956).

Abnormal sensitivity to the Hering-Breuer afferent impulses normally generated in the lung during expansion and collapse may be responsible for the sensation, complained of by some psychoneurotic patients, that they "need to but can't take a deep breath." It is suggested by some authors that, in a similar manner, an exaggerated discharge of these impulses from the congested and more rigid lungs augments the dyspnea during episodes of congestive heart failure.

Orthopnea. Patients with moderate to severe cardiac disease, especially with failure at rest, experience less dyspnea when sitting up leaning over a bed table or when in a semi-reclining position than when they are in a horizontal position. The degree of such orthopnea is often expressed in terms of the number of pillows required by the patient. The exact mechanism by which elevation of the cephalad part of the body reduces dyspnea is not known. In the horizontal position,

such patients have an arterial blood oxygen tension that is lower than normal. Factors that contribute to this condition are impaired mechanical respiration resulting from undue elevation of the diaphragm; increased rigidity of the lungs and lessened negativity of the intrapleural pressure caused by the pulmonary congestion; and impaired gaseous exchange resulting from increased pulmonary edema. The latter are probably caused by the elevated pressures in the right atrium and pulmonary trunk. In the normal person, recumbency is accompanied by an increased cardiac output which is thought to be caused by elevation of right atrial pressure by mobilization of fluid from the previously dependent parts of the body. Failure of the left ventricle to handle the increased venous return and right ventricular output would be a primary cause of increased pulmonary congestion and edema when recumbent.

Fever. Moderate elevation of body temperature, in proportion to the degree of congestive failure, has been reported. In these patients the fever could not be attributed to infection. In patients with congestive failure, fever is associated with subnormal cutaneous temperatures, whereas in infections, fever is associated with elevated cutaneous temperatures. The fever in congestive failure may be attributed to impaired transport of heat to the body surface, owing to (1) decreased cardiac output relative to heat production, and (2) cutaneous vasoconstriction (Altschule, 1949). However, it should be remembered that an elevation of body temperature may induce heart failure, especially if it occurs as a result of a hot, humid environment which makes it impossible for the patient adequately to eliminate heat. Such patients may suffer from dyspnea and apprehension (Burch, 1946).

Heart Strain. The term "heart strain" has been used by various authors with a variety of meanings. By some it has been used to imply acute distress, equivalent possibly to the type of "strain" which could produce acute ventricular dilatation. The electrocardiographic records published by most investigators (Burch and Winsor, 1945; Wiggers, 1949)

appear, on the other hand, to correspond more closely to those noted in authenticated cases of ventricular hypertrophy without acute dilatation. It would seem better to eliminate the term heart strain and refer to axis deviation or to heart position, to ventricular hypertrophy, or to acute ventricular dilatation (associated in many cases with some relative ischemia of the dilated ventricle).

Ventricular Hypertrophy. Ventricular hypertrophy occurs as a physiologic response to any condition which produces ventricular dilatation. In the absence of coronary artery disease, such dilatation results from any factor that increases the work load on the heart. Conditions, such as aortic valvular stenosis or insufficiency and systemic arterial hyperten-

sion, commonly lead to predominant left ventricular hypertrophy while abnormalities, such as mitral stenosis and pulmonary arteriolar sclerosis, lead to predominantly right ventricular hypertrophy.

Acute Ventricular Dilatation. Acute dilatation of a ventricular chamber presumably may occur whenever the heart goes rapidly into failure, because of mechanical overload. Such dilatation may occur in either chamber. It is likely to be superimposed upon a chamber already hypertrophied by an increased work load, occasioned by the same factors which ultimately lead to the acute failure. The acute dilatation will be associated with an elevated myocardial metabolic demand which the coronary vessels may not be able to meet.

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Congenital Malformations of the Heart and Great Vessels

A. Malformations of the Atrial Septal Complex

JESSE E. EDWARDS

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INTERATRIAL COMMUNICATIONS

INTERATRIAL COMMUNICATIONS may be subdivided into (1) valvular-competent, patent foramen ovale; (2) atrial septal defect, and (3) large communication between coronary sinus and left atrium. The last is not a true atrial septal defect and will be discussed only in the differential diagnosis.

Valvular-Competent, Patent Foramen Ovale

In about 20 to 25 per cent of normal adult human hearts it is possible to pass a probe from the right atrium into the left (Scammon and Norris, 1918; Patten, 1938, Wright *et al.*, 1948), even though no functional interatrial communication exists. The probe passes from right to left obliquely upward from the fossa

ovalis to, and beside, the valve of the foramen ovale (Figures VI-1a, b and VI-2). A foramen ovale that is functionally closed by a competent valve, preventing return flow from the left to the right atrium, has been termed "probe-patency of the foramen ovale" (Patten, 1931). Kirklin and associates (1955) and Weidman and his associates (1957) prefer the more definitive term, *valvular-competent, patent foramen ovale*. This condition should logically be regarded as a variant of the normal both because of its frequency and because no blood will pass through the vestigial channel unless the postnatal atrial pressure-relations are abnormal. Normally the pressure in the left atrium exceeds that in the right (Little *et al.*, 1949; Opdyke and Brecher, 1950); the

valve of the foramen ovale is pressed against the rest of the atrial septum and no blood is shunted from one atrium to the other. If the pressure in the right atrium exceeds that in the left, blood may flow from the right atrium into the left (Gross, 1934), as it did during fetal life.

Such a condition is encountered in pulmonary embolism when the increased resistance to pulmonary flow leads to increased pressure in the right ventricle and ultimately in the right atrium. If the blood entering the right atrium from the great veins contains more emboli, some of these may pass into the left atrium by way of the incompletely closed channel at the foramen ovale. In this way, it is possible for peripheral arteries to be occluded by emboli originating in the right atrium or one of its tributary veins. Passage of emboli across the atrial septum is termed *paradoxical embolism*. (See page 282.)

Other conditions, all associated with hypertrophy of the right ventricle, in which blood is shunted from the right to the left atrium in the presence of a valvular-competent foramen ovale,

include pulmonary valvular stenosis (Selzer and Carnes, 1953) and acquired pulmonary hypertension of unknown etiology (Shepherd *et al.*, 1957). Earl H. Wood and I have observed patients with ventricular septal defect (unpublished) in whom a right-to-left shunt through a valvular-competent foramen ovale had been demonstrated by the dye-dilution technique.

In cardiac catheterization of patients with valvular-competent foramen ovale, passage of the catheter through this normal tract may lead to a false diagnosis of true atrial septal defect. Further passage of the catheter by this route into a pulmonary vein may then give the false impression of the presence of anomalous pulmonary venous connection. Owing to the close relationship of the orifice of the inferior vena cava to the foramen ovale (Figure VI-2), if a catheter is introduced through the inferior vena cava, it is more likely to pass through a patent foramen ovale of this type than if it is introduced through the superior vena cava.

Atrial Septal Defect

Communications between the atria as a re-

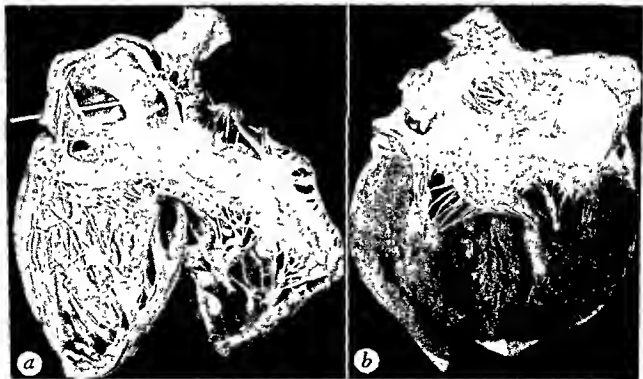


Figure VI-1. Valvular-competent, patent foramen ovale. *a*. Right side of heart. The probe has passed through the orifice of the inferior vena cava and has disappeared into the left atrium. The raised tissue around the foramen ovale is the limbus of the fossa ovalis. Beneath the fossa ovalis lies the orifice of the coronary sinus and inferior to that, the tricuspid valve. The superior vena cava is seen extending from the upper end of the specimen. *b*. Left side of heart. The probe which has disappeared from view in *a* appears in the left atrium as it pushes the valve of the foramen ovale to the left (right side in the illustration).



Figure VI-2. Relationship of inferior caval orifice to valvular-competent, patent foramen ovale. This view is taken from orifice of inferior vena cava. The dividing crest represents the anterior edge of the limbus of the fossa ovalis. The valve of the foramen ovale lies to the left of this structure. It is evident from this view that the inferior caval stream is directed toward both atria when a valvular-competent, patent foramen ovale exists. From the heart of an infant 4 months old. (From Swan and associates, 1954. Reproduced by permission of the authors and Grune & Stratton, Inc.)

sult of deficiency of septal tissue are classified as *atrial septal defects*. These are of various anatomic types.

PATHOLOGIC ANATOMY

Patency of Foramen Ovale. The common or "usual" variety of atrial septal defect may be regarded as valvular incompetence of the

foramen ovale. (See Developmental Basis of Atrial Septal Defects.) This defect has frequently been inappropriately named "defect of septum secundum." Although deficiency of septum secundum may contribute to the defect, usually septum primum is also involved in the deficiency. Defects at the foramen ovale less than 1 cm. in diameter in adults seldom are clinically significant. Those of clinical consequence may measure up to 4 cm. in diameter. The defect may be a single unguarded opening or it may be crossed by a lacework of tissue (Figure VI-3).



Figure VI-3. Atrial septal defect at region of foramen ovale, viewed from left. The defect results from a combination of shortness and perforation of the valve of the foramen ovale. From a woman 37 years of age.

The common variety of atrial septal defect is so placed that its center lies about midway between the orifice of the superior vena cava above and the base of the tricuspid valve below (Figure VI-4). Functionally, however, the defect is in closer relationship to the inferior vena cava than to the superior vena cava. The defect lies just anterior to the inferior caval orifice and above the ostium of the coronary sinus. As one looks into the atrial portion of the heart from the orifice of the inferior vena cava, a crest of muscle is evident beyond the caval channel (Figure VI-5), the anterior edge of the septal defect. The stream of inferior vena caval blood probably is split at this crest, part passing toward the tricuspid valve and part being directed into the left atrium.

In some cases the posterior boundary of the defect has no rim of septal tissue, the boundary of the defect being formed by the posterior atrial wall at the imaginary line where the left and

right atria join. The valve of the inferior vena cava lies just to the right of the plane of the atrial septal defect. In hearts with no posterior septal rim and a well-developed valve of the inferior vena cava (eustachian valve), the anterior edge of the latter may be mistaken for the posterior rim of an atrial septal defect by the surgeon's palpating finger (Hickie, 1956). Should the anterior edge of the valve be sewn to the anterior edge of the atrial septal defect, the entire inferior caval stream would be diverted into the left atrium (Figure VI-4).

Important differences exist between the right and left pulmonary veins in their relationship to atrial septal defects at the foramen ovale (Figure VI-6). The orifices of the right pulmonary veins and the streams of their blood lie just to the left of the atrial septum and thus are close to the defect, while the orifices of the left pulmonary veins and their blood streams lie as far removed from the atrial septum and its defects as is possible.

Defects in Lowermost Portion of Atrial

Septum (Persistent Common Atrioventricular Canal). Defects in the lowermost portion of the atrial septum in our experience are always associated with malformations of the atrioventricular valves (Rogers and Edwards, 1948; Wakai and Edwards, 1956). It is claimed that on rare occasions the septal defect may exist with structurally normal valves (Blount *et al.*, 1956). The defect may be viewed as a *persistence* of the fetal interatrial ostium primum and is often so termed. Some have referred to it as a "defect of the septum primum," but this is an inappropriate term because the developmental basis for the defect may include deficiency of interatrial septum secundum as well as of septum primum. In all cases, the atrial septal defect has a similar appearance. It lies below the fossa ovalis and its upper edge is crescent-shaped. The lower boundary of the atrial septal defect is formed by atrioventricular valvular



Figure VI-4. Atrial septal defect at region of foramen ovale without a posterior rim of tissue. *a*. Right side of heart. The probe extends from the inferior caval orifice into atrial septal defect. The tissue at the point of arrow, which appears from this perspective as though it were the posterior edge of the atrial septal defect, is in reality the valve of the inferior vena cava. The ostium of the coronary sinus (C.S.) lies inferior to the atrial septal defect. *b*. Left side of same heart. At the point of arrow is the anterior edge of the valve of the inferior vena cava. The inferior caval orifice (I.C.) lies to the left of the valve of the inferior vena cava (to the right in the illustration). It is evident that, if the surgeon mistakes the anterior edge of the valve of the inferior vena cava for the posterior rim of the atrial septal defect and sews it to the anterior edge of the atrial septal defect, the inferior vena caval stream would be directed entirely into the left atrium.

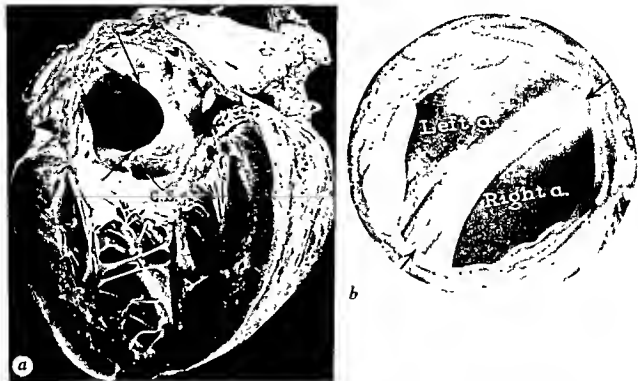


Figure VI-5. Atrial septal defect at foramen ovale, in a woman 48 years old with pulmonary hypertension. *a.* Conventional view of right side of heart, showing large atrial septal defect. The anterior edge of the defect lies between the points of the arrows. The coronary sinus (C.S.) lies inferior to the defect. The position of the orifice of the inferior vena cava is indicated by the white dotted oval area. The right ventricle is hypertrophic. *b.* View of interior of heart through orifice of inferior vena cava. In this illustration the heart has been oriented as it lies in the body. The crest of tissue, lying between the points of the arrows, corresponds to that between the arrows in *a*, and is the anterior edge of the atrial septal defect. It may be said to represent a dividing crest as it lies in the path of the stream of blood entering the heart through the inferior vena cava. The left atrial cavity lies to the left and above this crest, while the right atrium lies to the right and below. It is evident from this illustration how readily inferior vena caval blood may be shunted from right to left in atrial septal defect. Similar anatomic relations with regard to the inferior caval orifice and valvular-competent, patent foramen ovale are illustrated in Figure VI-2.

tissue (Peacock, 1846-48; Gunn and Dieckmann, 1927, Robson, 1931; Robinson, 1941; Moragues, 1943).

Cases of persistent common atrioventricular canal may be subdivided into (1) complete, (2) partial and (3) transitional forms (Wakai and Edwards, 1956).

Complete type of persistent common atrioventricular canal. When the heart is dissected in a routine manner, the anterior or aortic leaflet of the mitral valve and the septal leaflet of the tricuspid valve are each split into an anterior half and a posterior half (Figure VI-7*a, b*). Instead of a mitral valve and a tricuspid valve, one atrioventricular valve is common to both sides of the heart. What had been interpreted as the anterior halves of the split leaflets of the mitral and tricuspid valves is in reality an anterior leaflet of a common atrioventricular valve. Likewise, the

posterior halves of the split leaflets are continuous and in reality form a posterior leaflet of the common valve. Usually two lateral leaflets on the right side represent the elements which normally form the anterior and posterior tricuspid leaflets. On the left side the common valve has a lateral leaflet, which in turn is the counterpart of the posterior mitral leaflet of normal hearts. Shaner (1949) has observed this malformation in pig embryos.

The chordae tendineae of the anterior common leaflet are attached to two different regions. Those attached to the left side of the valve insert into the anterior papillary muscle of the left ventricle, while those attached to the right side of the leaflet insert into the corresponding papillary muscle in the right ventricle (Figure VI-7). The chordae tendineae of the common posterior leaflet are usually short. Some are attached to the crest of the underlying muscular ventricular septum and to

Figure VI-6 Viewed from behind, left side of heart with a simulated atrial septal defect (A.S.D.) at fossa ovalis. The left pulmonary veins (L.P.V.) lie removed from the atrial septum. The orifices of the right pulmonary veins (R.U.P.V. and R.L.P.V.) lie close to the atrial septum and to the simulated atrial septal defect. The arrows from the left pulmonary veins indicate that most of the blood from the left lung is carried through the mitral valve into the left ventricle. The blood from the right pulmonary veins, on the contrary, crosses the zone where the atrial septal defect lies and constitutes the major portion of the blood shunted from left to right in the usual example of atrial septal defect. (Modified from Swan and associates, 1953, and reproduced with their permission.)

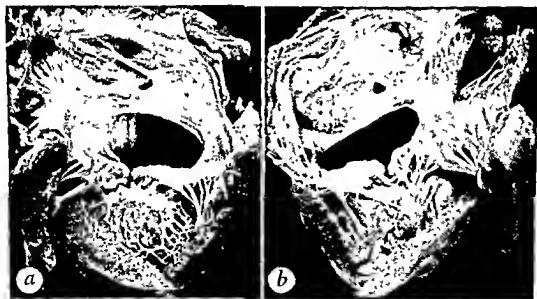
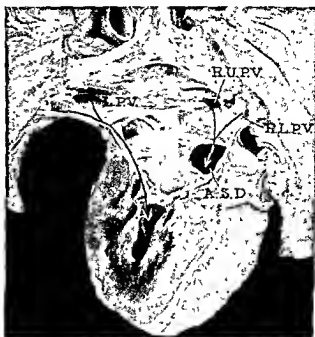


Figure VI-7. Complete type of persistent common atrioventricular canal in female infant 2½ months old. (From Rogers and Edwards, 1948. Reproduced by permission of C. V. Mosby Company.) *a.* Left side of heart. Above the cleft anterior leaflet of the mitral valve is a crescent-shaped defect in the inferior part of the atrial septum. The latter represents persistence of the interatrial foramen primum. Above this, the foramen ovale shows a mild degree of patency on the basis of a short valve of the foramen ovale. The chordae tendineae of the ventral part of the cleft anterior leaflet of the mitral valve are inserted into the anterior papillary muscle of the left ventricle. Some of the chordae of the posterior half of the leaflet are inserted into the ventricular septum. *b.* Right side of heart. The septal leaflet of the tricuspid valve shows a cleft similar to that in the anterior leaflet of the mitral valve shown in *a.* The lower limbus of the fossa ovalis is deficient. This supports the view that persistence of the interatrial foramen primum represents deficiency, not only in septum primum but also in septum secundum. The additional defect in the region of the foramen ovale which was shown in *a* is also illustrated. Right atrial dilatation and right ventricular hypertrophy are present.



Figure VI-8. Left ventricle and ascending aorta, from a male infant, aged 5 months, with complete type of persistent common atrioventricular canal. The anterior leaflet of the mitral valve has been reflected to the right of the illustration in such a way as to show the lack of attachment between the ventricular side of this leaflet and the ventricular septum. Such deficiencies are common not only beneath the anterior, but beneath the posterior leaflets of the common atrioventricular valve, in the complete variety of the malformation. Such deficiencies create an interventricular communication, in addition to the interatrial communication. The deficiency of the membranous portion of the ventricular septum, which is common in the malformation, also is illustrated. (From Rogers and Edwards, 1948, Reproduced by permission of C. V. Mosby Company.)

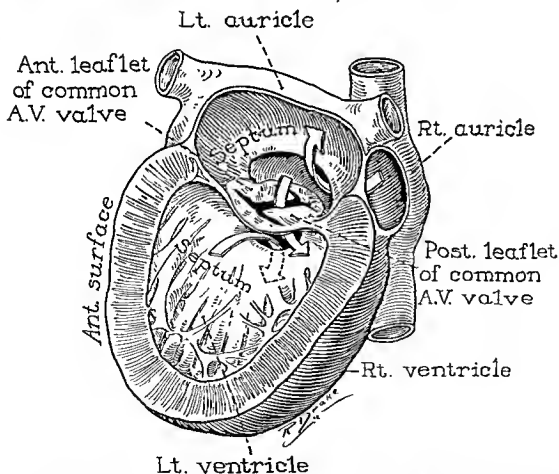


Figure VI-9. Complete variety of persistent common atrioventricular canal. The lateral walls of the left atrium and ventricle have been removed. The atrioventricular canal is common to both sides of the heart. It is guarded by a single valve possessing large anterior and posterior leaflets, two right lateral leaflets and a left lateral one. There is an interatrial communication above the common valve and interventricular communication below it. (From Rogers and Edwards, 1948. Reproduced by permission of C. V. Mosby Company.)

adjacent portions of the respective sides of the septum in each ventricle or to papillary muscles. The chordae of the lateral leaflets are attached to papillary muscles corresponding to those to which the anterior and posterior tricuspid leaflets and the posterior mitral leaflets attach normally. Shortness of the posterior common leaflet and chordae probably accounts for insufficiency of the valve during life.

Usually, in this condition, there is a concavity of the posterior part of the muscular ventricular septum inferior to the space between the free edges of the anterior and posterior leaflets of the common atrioventricular valve. Through this concavity the ventricles communicate. The two ventricles also communicate in two other areas: inferior to the posterior leaflet of the common valve, and inferior to the anterior leaflet. Beneath the posterior leaflet, there is often no membrane of continuous fusion between the leaflet and the underlying ventricular septum. Instead, numerous chordae may run between the under surface of the posterior leaflet and the upper edge of the ventricular septum. Between the chordae are spaces through which the two ventricles communicate freely.

Beneath the anterior leaflet also, complete fusion with the ventricular septum may be absent,

permitting free communication between the two ventricles (Figures VI-8 and VI-9). *Lack of complete fusion* of the anterior and posterior leaflets of the common atrioventricular valve with the ventricular septum is the basis for interventricular communication (Moragues, 1943; Rogers and Edwards, 1948, Lewis *et al.*, 1955). Inferior and anterior to the anterior leaflet of the common valve, the ventricular septum usually has a wide concave deficiency which is associated with absence of the membranous portion of the ventricular septum.

Partial form of persistent common atrioventricular canal. The partial form usually has no anatomic interventricular communication, although functionally blood from the left ventricle may appear to enter the right ventricle, possibly as a consequence of mitral insufficiency and the interatrial communication. The tricuspid valve is devoid of a cleft and is intact around the entire tricuspid orifice (Figure VI-10a). The anterior leaflet of the mitral valve, however, has a cleft at its center (Figure VI-10b). The developmental explanation is that the atrioventricular endocardial cushions were deficient mainly along their left side, thus causing the cleft in the mitral valve, on the right side, the ventral and dorsal atrioventricular endocardial cushions fused with

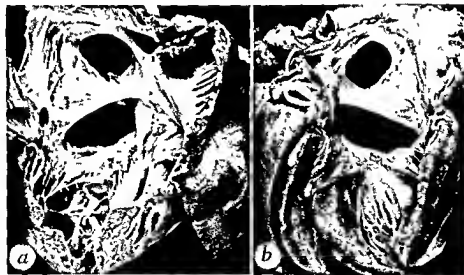


Figure VI-10. Partial type of persistent common atrioventricular canal, in male infant 6 months old. (From Rogers and Edwards, 1948. Reproduced by permission of C. V. Mosby Company.) *a.* Heart viewed from right. The defect in the inferior part of the atrial septum is characteristic of that in persistent common atrioventricular canal. The tricuspid valve is essentially normal. In addition, a second defect is present in the region of the foramen ovale. The limbus of the fossa ovalis is not identifiable. *b.* Left side of heart. Beneath the defect in the inferior part of the atrial septum the anterior leaflet of the mitral valve is cleft, except at its base. The defect of the atrial septum, in the region of the foramen ovale, is also shown.

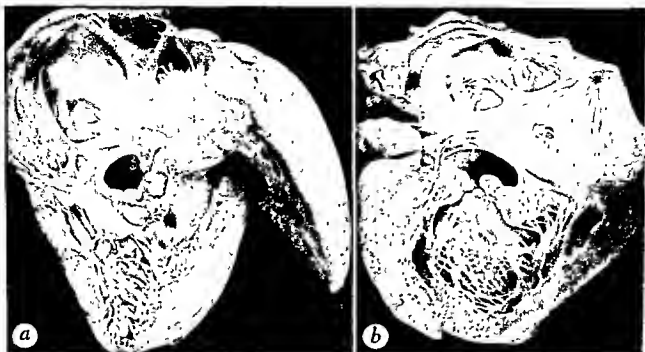


Figure VI-11. Transitional variety of persistent common atrioventricular canal. From a boy 3½ years old. *a*, Right side of heart. A characteristic defect is present in the lowermost portion of the atrial septum. The septal leaflet of the tricuspid valve shows a cleft, but a bridge of tissue extends from the anterior to the posterior component and lies immediately above the ventricular septum. The region of the fossa ovalis is normal and the foramen ovale is not patent. *b* Left side of heart. There is a cleft in the anterior leaflet of the mitral valve but, as in the tricuspid valve, a bridge of tissue joins the two components of the leaflet just above the ventricular septum. This heart had no interventricular communication. The left ventricle and aortic valve are illustrated in Figure VI-12.

each other to form a continuous tricuspid valve.

A defect exists between the two sides of the heart, which is almost entirely in the atrial portion. The atrial component of the defect is similar to that in the complete form, with one exception. In the complete form, the lower portion of the atrial component of the defect is continuous with the space between the anterior and posterior leaflets of the common valve and with interventricular communications of varying sizes, while in the partial form, the lower edge of the atrial defect is formed by the intact septal leaflet of the tricuspid valve (Figure VI-10*a*). In the complete form, the opening of what conventionally is called "the mitral orifice" is continuous with that of the tricuspid orifice, while in the partial form, the mitral orifice extends abnormally into the cleft of its anterior leaflet but the right and left atrioventricular orifices are divided by the intact septal leaflet of the tricuspid valve.

In all forms (complete, partial and transitional), beneath the atrioventricular valves the ventricular septum has an unusual, broad sweeping concavity which extends into the subaortic region. Usually in the partial type, the ventricu-

lar sides of the anterior mitral leaflet and of the septal tricuspid leaflet are attached, by tissue resembling fused chordae, to the upper aspect of the concavity in the ventricular septum, thus preventing anatomic interventricular communication. The fused chordlike tissue fills the space ordinarily occupied by the membranous septum. From the right side, it is apparent that the fused tissue joining the atrioventricular valves to the ventricular septum inserts along the postero-inferior aspect of the crista supraventricularis.

Transitional varieties of persistent common atrioventricular canal. Wakai and Edwards (1956) observed anatomic transition between the complete and the partial varieties in 3 hearts, characterized by clefts not only in the anterior leaflet of the mitral valve, but also in the septal leaflet of the tricuspid valve. This arrangement is similar to the complete form. In each of these 3 cases, however, a narrow bridge of valvular tissue joined the anterior half of each of the two cleft leaflets with their respective posterior halves just above the ventricular septum (Figures VI-11 and VI-12), the bridge of tissue precluding communication of the mitral and tricuspid orifices.

Defects Superior to Fossa Ovalis (with Partial Anomalous Pulmonary Venous Connection). Defects of the atrial septum superior to the fossa ovalis, formerly thought to be rare (Peacock, 1878), are observed in about 10 per cent of patients operated on for atrial septal defect (Swan *et al.*, 1957). These defects are usually smaller than those at the fossa ovalis and their size has the same general range as those which are part of the persistent common atrioventricular canal.

Various names have been applied to this defect, including "high atrial septal defect" (Lewis *et al.*, 1955), "superior marginal defect" (Watkins and Gross, 1955) and "sinus venous type of atrial septal defect" (Ross, 1956). The defect lies close to the ostium of the superior vena cava (Figure VI-13) and this vessel may straddle it. No margin of septum is present superior to the defect. Associated with the defect is an anomalous connection of the pulmonary veins of the upper lobe of the right lung and, at times also, of the right middle and inferior pulmonary veins with the atrium or superior vena cava (Hepburn, 1887, Ingalls, 1907, Van Cleave, 1931, Swan *et al.*, 1957). The left pulmonary veins join the left atrium in a normal manner. The region of the foramen ovale usually is developed normally, although rarely a defect in this region may coexist with one superior to the fossa ovalis. Single or multiple anomalous pulmonary veins connect with either the superior vena cava or the right atrium near the orifice of the superior vena cava.

Defects Posterior to Fossa Ovalis (with Partial Anomalous Pulmonary Venous Connection). The author has observed an atrial septal defect which lay posterior to the fossa ovalis. The defect was just to the left of the orifice of the inferior vena cava and above the orifice of the coronary sinus. All 3 right pulmonary veins connected anomalously with the posterior wall of the right atrium. The foramen ovale was valvular-competent and patent (Figure VI-14).

Defects Involving Entire Atrial Septum (Single Atrium). Less common than the defects already described is an atrial septum that is either completely defective or so vestigial as to be regarded as absent. The atrium is single but has two auricular appendages (Young and Robinson, 1907-08).

Cor trifolore bicentricularis is the term ap-

plied to a heart with a single atrium but an intact ventricular septum. The functional derangement is similar to that in large atrial septal defects. The predominant direction of flow of blood is toward the right through the tricuspid valve, but the normal differential of pressure between the two ventricles is maintained. Though the mitral and tricuspid orifices are usually separate, in the case reported by Cunningham (1948) the heart had a common atrioventricular valve.

Cor biloculare. When both the atrial and ventricular septa are absent, the chief factor of significance is the absence of differential ventricular pressures. The ejectile force is the same for blood flowing to the pulmonary and to the systemic circulations. In this respect, cor biloculare is identical with a heart having an atrial septum but no ventricular septum (cor trifolore biatriatum).

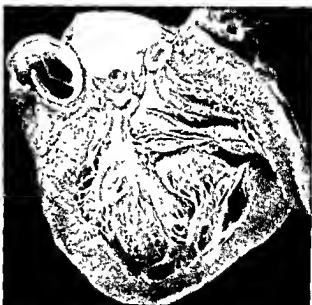


Figure VI-12. (From same case as Figure VI-11.) Left ventricle and aortic valve in transitional variety of persistent common atrioventricular canal. A portion of the cleft in the anterior leaflet of the mitral valve is shown. The anterior portion of the anterior leaflet of the mitral valve is intimately adherent to the muscular portion of the ventricular septum, filling the gap caused by absence of the membranous septum. In addition, some deficiency of the muscular portion of the ventricular septum is represented by the concavity at the site of the attachment of the mitral valve to it. The intimate adherence of the mitral valve to the underlying ventricular septum precludes an inter-ventricular communication, even though there is a basic deficiency in the ventricular septum. Note the areas of raised endocardial tissue in the left ventricle which seem to represent lesions caused by trauma from streams of blood. (From Wakai and Edwards, 1956.)



Figure VI-13. Atrial septal defect superior to fossa ovalis and associated with anomalous right upper pulmonary veins. (From Swan and associates, 1957. Reproduced by permission of the authors and Grune & Stratton, Inc.) *a*, Right atrium. The atrial septal defect lies in the upper portion of the atrial septum between points of arrows and superior to the fossa ovalis (F.O.). The right atrial orifice of the superior vena cava (S.V.C.) is close to the atrial septal defect. The probe lies in the azygos vein. Two veins from the upper lobe of the right lung connect anomalously with the superior vena cava. G.S. indicates coronary sinus. *b*, Left side of heart. The defect is shown between the points of the arrows. The area marked Os. II is a normal structure representing interatrial ostium secundum. The veins from the right middle lobe (R.M.L.V.) and the veins from the right lower lobe (R.L.L.V.) connect normally with the left atrium. The left pulmonary veins (L.P.V.) join to form a common trunk which enters the left atrium in a normal manner.

INCIDENCE

Incidence of All Types of Atrial Septal Defect. At the Mayo Clinic, among 550 pathologic specimens with major malformations of the heart and great vessels from persons of all ages, 44 (8 per cent) had an atrial septal defect, an additional 28 (5 per cent) had a persistent common atrioventricular canal. Among 13,883 necropsies performed at the Los Angeles County Hospital from 1938 through 1947, 209 had congenital malformations of the heart, of which 61 exhibited an atrial septal defect (Maronde, 1950). Among 200 patients with congenital heart disease studied clinically, either by cardiac catheterization or by angiography, Wood (1950) found 35 (17.5 per

cent) with atrial septal defect. In 11 of a series of 202 necropsies on children, Disenhouse and associates (1954) found atrial septal defect (presumably not including persistent common atrioventricular canal). Keith and Forsyth (1951) found that, among infants and children, atrial septal defect was the sixth most common cardiac malformation in clinical studies and the thirteenth in frequency in necropsy material. Among 185 necropsies on patients with congenital cardiac disease, 4 had atrial septal defect.

The lower incidence of atrial septal defect in series restricted to the young, compared to findings in material from persons of all ages, reflects the tendency of patients with this condition to live to adult life (see Prognosis, page 275).

Relative Incidence of Various Types of Atrial Septal Defect. The 550 hearts with congenital cardiac malformations in the pathologic collection of the Mayo Clinic include 41 with atrial septal defect of the usual variety at the fossa ovalis, and 28 with persistent common atrioventricular canal. Defects in 17 of the latter are of the complete type; in 7, of the partial type, and in 4, of the transitional type. In 3 additional cases, the right pulmonary veins are connected anomalously, in 2 of these cases, the defect is situated superior to the fossa ovalis and in the third, posterior to the fossa ovalis. Lewis and associates (1955) reported that, in 23 of 35 patients operated upon for atrial septal defect, the defect was at the foramen ovale, in 6 the defect was part of the complex known as "persistent common atrioventricular canal" and in 5 the defect was in the upper portion of the septum and associated with partial anomalous pulmonary venous connection. The remaining patient had a large defect which,

in effect, probably represented complete absence of the septum. Watkins and Gross (1955) observed 43 cases of atrial septal defect at operation. According to our classification, in 33 the defect was in the region of the foramen ovale, in 4, part of the persistent common atrioventricular canal; in 4 in the upper part of the atrial septum, and in 2 hearts the septum was absent. Among 90 patients operated on for atrial septal defect, Swan and associates (1957) reported that in 6 the defect was superior to the fossa ovalis and associated with anomalous connection of some or all of the right pulmonary veins.

SEX DISTRIBUTION

Atrial septal defect is generally thought to be twice as common in female patients as in males.

Of 43 pathologic specimens with atrial septal defect at the Mayo Clinic in which the sex was



Figure VI-14. Atrial septal defect posterior to fossa ovalis, associated with anomalous connection of the right pulmonary veins. From a man 34 years old with moderate pulmonary hypertension. *a*, Right side of heart. The probe lies in the foramen ovale which shows valvular-competent patency. Posterior to this lies the atrial septal defect. This lies just in front of the orifice of the inferior vena cava (I.C.) which has been opened. Posterosuperior to the atrial septal defect (within triangle) are 3 pulmonary veins representing the entire venous supply of the right lung. In contrast to the position of the defect in Figure VI-13, here the defect is removed from the superior caval orifice (S.C.). C.S. represents coronary sinus. The right ventricular chamber is dilated and its wall is hypertrophied. *b*, Left side of heart. The probe has entered the left atrium through a valvular-competent, patent foramen ovale. Posterior to it and at essentially the same supero-inferior level lies the atrial septal defect. The left pulmonary veins (L.P.V.) enter the left atrium in a normal manner. The right lower pulmonary vein (R.P.V.) is seen in this perspective but it does not enter the left atrium, having entered the right atrium anomalously as illustrated in *a*.

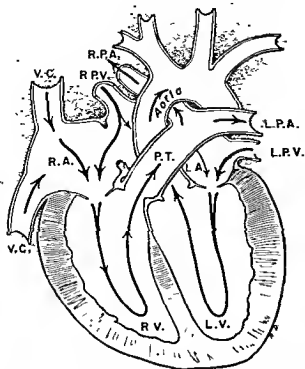


Figure VI-15. The intracardiac circulation in atrial septal defect at the foramen ovale. The major shunt is left to right and predominantly from the right lung. Lettering is self-explanatory.

known, in 27 the patient was female and in 16, male. In several clinical studies of infants or children with atrial septal defect, the sex incidence was as follows. Wood (1950), 35 patients, 23 females and 12 males; Braudo and associates (1954), 32 children, 25 girls and 7 boys, Dishenhouse and associates (1954), 21 patients, 12 female and 9 male, Weidman and associates (1957), 71 patients, 49 female and 22 male. In the malformation known as *persistent common atrioventricular canal*, the sex distribution is about equal (Wakai and Edwards, 1956).

FUNCTIONAL AND STRUCTURAL EFFECTS IN UNCOMPLICATED CASES

Circulation in Fetus and Postnatal Changes. In the normal fetus (see Chapter 11) a substantial amount of blood from the inferior vena cava is shunted across the foramen ovale into the left atrium (Barcroft, 1935, 1936; Barclay *et al.*, 1939, 1941, 1944). In fetuses with atrial septal defects, regardless of type, it is also reasonable to suppose that the transatrial flow is normal. After birth, in patients with an atrial septal defect, blood

may flow in either direction. The occurrence of cyanosis during early infancy in some patients with atrial septal defect suggests that a right-to-left shunt may predominate during this early period. Later, a left-to-right shunt becomes established.

Nature and Causes of Shunts. In uncomplicated cases and regardless of the anatomic type of atrial septal defect, the direction of the shunt across the defect is predominantly from the left to the right atrium (Figure VI-15).

This has been amply demonstrated by catheterization studies (Brannon *et al.*, 1945; Courmand *et al.*, 1947, Swan *et al.*, 1956; Weidman *et al.*, 1957). Evidence of this shunt is also apparent in angiocardigraphic studies which show "delayed emptying" of the right atrium. This phenomenon is in reality a manifestation of re-opacification of this chamber (Lind and Wegelius, 1953). The volume of the left-to-right shunt may exceed by 2 to 4 times the volume of left ventricular output. The volume of left-to-right shunt in adults commonly averages 7 to 8 liters per minute, about twice the output of the left ventricle. Sometimes the systemic output is below normal but usually it is within normal limits (Weidman *et al.*, 1957). It has been suggested that the basis for this major shunt in atrial septal defect is the higher pressure in the left atrium during the postnatal state (Courmand *et al.*, 1947; Stead and Warren, 1947; Hickam, 1949, Little *et al.*, 1949).

In the presence of a large atrial septal defect, the heart, in effect, has but one atrium (Barger *et al.*, 1948), and the major direction of flow from the functionally common chamber will be in the direction of least resistance (Hull, 1949). The myocardium of both ventricles may be said to exert resistance to filling of the ventricles. The thicker the wall of the ventricle, the greater the resistance to its filling. Some time after birth, the left ventricle becomes thicker than the right, not only in persons with normal hearts but also in those with atrial septal defect. Since the right ventricle will then exert less resistance to filling than the left ventricle, the blood from the functionally common atrium will be shunted mainly to the right ventricle.

Other factors which may favor preferential flow into the right ventricle are (1) the long, narrow nature of the left ventricle contrasted to the shorter, broader chamber of the right, and

(2) the greater width of the orifice of the tricuspid valve than that of the mitral valve. In these cases of atrial septal defect, regardless of the great volume of pulmonary blood flow, the pulmonary arterial pressure is essentially normal. This pressure phenomenon reflects the low pulmonary vascular resistance. (See Complications, page 276.)

Blood may also be shunted from right to left through the atrial defect, but in uncomplicated cases the amount shunted is small (Hickam, 1949) and the desaturation is usually insufficient to be detectable by manometric means. Swan and his associates (1954) demonstrated such minor shunts by dye-dilution tests. They also demonstrated that the right-to-left shunt usually is derived mainly from the inferior vena cava with only minor, if any, contribution from the superior vena cava. This seems to result from the combination of streamlining of the caval streams and the close relations of the inferior vena caval orifice to the septal defect (Figure VI-5).

Associated Structural Changes. The left-to-right major shunt in atrial septal defect involves both atria and the right ventricle. As a consequence, the right atrium and the right ventricle show significant enlargement. In uncomplicated cases, however, the thickness of the wall of the right ventricle is not increased. This type of right ventricular enlargement is associated with electrocardiographic evidence of right bundle-branch block

(Barber *et al.*, 1950; Carloti *et al.*, 1952; Smull and Lamb, 1952). The left ventricle is of normal size. Although the left atrium carries blood received in the shunt, it is not enlarged, probably because this chamber is readily decompressed by the defect. The pulmonary trunk and its branches are wider than normal and reflect the great volume of blood flow through these vessels (Figure VI-16a). The aorta also reflects the volume of flow through this vessel and its lumen is of normal caliber or is somewhat narrower than usual. The small pulmonary vessels are essentially normal in uncomplicated cases.

Clinical Manifestations (Taussig *et al.*, 1938, Bedford *et al.*, 1941; Wood, 1950, Braudo *et al.*, 1954; Disenhouse *et al.*, 1954). In the uncomplicated state the patient is acyanotic and may be entirely asymptomatic. Some patients may suffer from dyspnea on exertion. Frequently a blowing systolic murmur is audible to the left of the sternum and maximal in the left intercostal space. This may be the only abnormal initial sign. The dilatation of the pulmonary trunk, with stretching and consequent rigidity of the pulmonary cusps, may contribute to relative stenosis of the pulmonary valve and to the murmur. A middiastolic murmur is frequently heard along the left sternal border (Blount *et al.*, 1954). This should not be confused with the diastolic murmur of mitral stenosis which is infrequent in



Figure VI-16. a Dilated pulmonary trunk and right ventricle, from a woman 37 years of age with atrial septal defect. The defect in the atrial septum is illustrated in Figure VI-3. b. Roentgenogram of thorax showing dilatation of pulmonary trunk and its branches.

patients with atrial septal defect (Blount *et al.*, 1954).

Leatham and Gray (1956) reviewed the subject of *heart sounds* in atrial septal defect. An accentuated first sound was attributed to closure of the tricuspid valve, and splitting of the second sound at the pulmonary region was related to delayed closure of the pulmonary valve. This delay may result from the right ventricle having a longer systole because it expels more blood than the left ventricle. Increased flow through the pulmonary valve was thought to be the cause of a left parasternal systolic murmur. It is doubtful whether the flow of blood through the atrial septal defect itself produces a murmur, in view of the large aperture and the small differences in pressure in the two atria.

Roentgenologically, the dilated pulmonary trunk and major pulmonary arteries are expressions of the excessive pulmonary blood flow (Figure VI-16*b*). Roentgenoscopic examination may reveal unusual pulsations of the hilar vessels, the so-called "hilar dance" (Roesler, 1934; Smull and Lamb, 1952). A causal relationship seems to exist between the frequent precordial bulging in patients with atrial septal defect and dilatation of the pulmonary trunk. Very likely the pulmonary arterial dilatation during the period of skeletal development is a factor in molding the shape of the thoracic cage.

The demonstration by *cardiac catheterization* of highly oxygenated blood in the right atrium suggests some type of atrial septal defect with left-to-right shunt (Brannon *et al.*, 1945), but is not necessarily diagnostic (page 275).

Distinguishing Features of Various Types of Atrial Septal Defect. Atrial septal defects, regardless of anatomic type, have in common certain basic functional and secondary structural effects. The various types of defects also have certain functional differences which are mainly detected by the study of dye-dilution curves obtained by injecting dye at different sites.

In defects representing patency of the foramen ovale, Swan and associates (1956) have shown that the blood shunted through the defect comes mainly from the right pulmonary veins (Figure VI-6). The inferior vena cava contributes more blood to this right-to-left shunt than does the superior vena cava (Swan *et al.*, 1954). These views are supported by the experimental work of Silver and associates (1956).

In defects that lie inferior to the fossa ovalis, the differences between the contributions made by the right and the left lungs to the left-to-right shunt are not as great as those just mentioned, although even here the right pulmonary veins tend to contribute more blood to the shunt than do the left pulmonary veins. The difference between the contribution made by the inferior and that made by the superior vena cava to a right-to-left shunt also is not as striking as in defects at the foramen ovale. Additional arterialization may occur in the right ventricle (Wakai *et al.*, 1956). Defects that lie inferior to the fossa ovalis are part of the malformation-complex known as persistent common atrioventricular canal. The partial type of this malformation has a cleft in the anterior mitral leaflet but usually no interventricular communication (Wakai and Edwards, 1956). In such cases, since the interatrial communication may be associated with mitral insufficiency (Brandenburg and DuShane, 1956), Lutembacher's syndrome may be falsely suspected (Cohen *et al.*, 1952).

In the complete type of persistent common atrioventricular canal the functional and clinical features may result principally from the associated interventricular communication, alone or in association with atrioventricular valvular insufficiency (Brandenburg and DuShane, 1956).

Defects that lie superior to the fossa ovalis produce distinctive functional features (Swan *et al.*, 1957). Half or even all of the pulmonary veins are connected anomalously to the right atrium or to the superior vena cava; preferential drainage of the right pulmonary blood into the right atrium may be even more striking than in defects at the fossa ovalis.

Perhaps a more clear-cut difference is a right-to-left shunt of significant proportions, to which the superior vena cava contributes more than does the inferior vena cava. Since the blood in the right-to-left shunt has a higher concentration of oxygen because of elements derived from the lung, desaturation of the peripheral blood may be slight. The paradox of a large right-to-left shunt in the presence of little peripheral desaturation clinically suggests a defect superior to the fossa ovalis, associated with partial anomalous connection of the pulmonary veins.

ASSOCIATED CONDITIONS

In the pathologic collection of the Mayo Clinic, Fontana (1957) observed 31 atrial septal defects without other cardiac malformations, not including persistent common atrioventricular canal, and

7 hearts had atrial septal defect associated with other independent malformations. In this material, ventricular septal defect was the most common malformation associated with atrial septal defect.

The author has examined the heart of a 1-year-old child, which had an atrial septal defect at the fossa ovalis, and in addition, stenosis of each of the pulmonary veins at its junction with the left atrium. Maronde (1950) found 2 cases of associated ventricular septal defect among 61 hearts with atrial septal defect.

Defects may be associated with *persistent common atrioventricular canal*. Wakai and Edwards (1956) found a large atrial septal defect in 1 of 5 hearts with the partial type of persistent common atrioventricular canal (see Figure VI-10). Among 14 hearts with the complete variety of common atrioventricular canal, 4 had associated large defects in the region of the foramen ovale. Sometimes serious malformations of the great vessels may be present. In 1 heart both great vessels arose from the right ventricle and the pulmonary valve was stenotic. A second heart had right ventricular infundibular stenosis.

Traditionally, *mongolian idiocy* has been associated with persistent common atrioventricular canal (Wurtz and Powell, 1948; Buzzi *et al.*, 1955). Apparently mongolian idiocy is more likely to be associated with malformation of the complete variety than with the partial or the transitional form. Most adult patients with the partial variety of malformation do not have mongolian idiocy. In 56 cases of this malformation reviewed by Rogers and Edwards (1948), mongolian idiocy was recorded in 17.

DIFFERENTIAL DIAGNOSIS

Many conditions may simulate the picture of atrial septal defect, including acyanotic conditions that are characterized by high pulmonary flow or pulmonary hypertension, or both. Major conditions include ventricular septal defect, patent ductus arteriosus, partial or total anomalous pulmonary venous connection, and idiopathic pulmonary hypertension.

Conditions, other than atrial septal defect, which on cardiac catheterization may have high oxygen-saturation of right atrial blood, include ventricular septal defect with tricuspid insufficiency, congenital communication between the left ventricle and right atrium, anomalous pulmonary

venous connection, or triatriatum with communication between the accessory chamber and the right atrium, aneurysm of aortic sinus rupturing into the right atrium, and congenital communication between a coronary artery and the right atrium or coronary sinus.

Unusually Large Communication between Coronary Sinus and Left Atrium. Normally small communications may exist between the coronary sinus and the left atrium. Rarely, as in the case reported by Craig (1952), such a communication may be so large as to constitute, in effect, an interatrial communication with functional features like those of true atrial septal defect. From the left side, the heart looks as though an atrial septal defect were present in the lowermost part of the atrial septum, just above the posteromedial commissure of the mitral valve. From the right side there is no defect, but the ostium of the coronary sinus usually appears large. The distance in the coronary sinus between the normal communication with the right atrium and the abnormal one with the left atrium is scant. The treatment is simple closure of the right atrial ostium of the coronary sinus.

PROGNOSIS

With the exception of the complete type of persistent common atrioventricular canal (see page 264), patients with atrial septal defect usually bear the defect well for many years, though cardiac failure may result during childhood (Braudo *et al.*, 1954; Disenhouse *et al.*, 1954). Most patients ultimately show deleterious effects as a result of the malformation. In some cases the defect is discovered incidentally after death from unrelated causes. Death may result from atrial septal defect in infancy and childhood, but most patients reach adult life.

In 19 cases studied at necropsy by Cosby and Griffith (1949), the average age was 49 years. Roessler (1934) reviewed 62 cases of atrial septal defect (Table VI-1). Excluding persons who died of unrelated conditions, the average age at death was 36 years. Braudo and associates (1954) reviewed necropsy data on 80 patients of all ages with atrial septal defect. In 35, death was related to the atrial septal defect, and the

TABLE VI-1

Age at Death in 62 Cases of Atrial Septal Defect *

Age in years	Cases	Per cent
0-10	5	8.0
11-20	8	12.9
21-30	15	24.2
31-40	9	14.5
41-50	10	16.1
51-60	10	16.1
61-70	3	4.8
71-75	2	3.3

* From Roesler (1934), by courtesy of the author, and the editor of Archives of Internal Medicine.

average age was 40 years (range 6 months to 77 years). In the remaining 45 cases in which death was not related to the malformation, the average age was 40.5 years (range 1 to 80 years). Conlshed and Littler (1957) reported 5 clinical cases in which ages ranged from 58 to 79 years. Isolated examples of unusually long survival in atrial septal defect have been reported (Tamower and Woodruff, 1936, Askey and Kahler, 1950, 72 years, Ellis *et al.*, 1950, 82 years, Stannus *et al.*, 1955, 70 years). In the Mayo Clinic's pathologic collection of atrial septal defects, 4 of the hearts with the usual variety of defect were from patients 70 years old or older.

The general remarks concerning atrial septal defect apply to patients with the partial variety of persistent common atrioventricular canal. Most patients with the complete variety die during the first year of life (Rogers and Edwards, 1948, Wakai and Edwards, 1956); rarely, the patient lives to adult life (Curtin, 1952, 58 years of age). The poor prognosis in most patients with the complete form of persistent common atrioventricular canal is probably related to frequent existence of an interventricular communication; associated incompetence of the atrioventricular valves may also cause cardiac failure at an early age.

COMPLICATIONS

The common complications of atrial septal defect are pulmonary hypertension, valvular disease, cyanosis, and cardiac failure. Sudden death and cerebral abscess are less common.

Pulmonary Hypertension. Among patients with atrial septal defect, cardiac catheterization indicates considerable variation in pulmonary arterial pressures. The pressure may be normal or only slightly elevated (systolic pressure of 40 mm. or less of mercury reported by Weidman *et al.*, 1957), or may even be higher than the systemic arterial pressure. Although there is no direct relationship between the pulmonary arterial pressure and the age of the patient, pulmonary hypertension is uncommon in children; pulmonary hypertension, when present, is usually seen in adults (Blount *et al.*, 1954; Disenhouse *et al.*, 1954; Kirklin *et al.*, 1956, Weidman *et al.*, 1957). Pulmonary hypertension is regarded, not as a natural accompaniment or inevitable consequence of atrial septal defect, but as a complication.

If pulmonary hypertension is absent, the right ventricle is primarily dilated; if pulmonary hypertension is present, the mass of muscle is obviously thickened. In atrial septal defect with pulmonary hypertension, the degree of hypertrophy of the right ventricle is similar to that in patent ductus arteriosus or ventricular septal defect, a feature that coincides with the similarity of the electrocardiogram in these conditions (Cosby *et al.*, 1952).

Pulmonary arterial pressure is an expression of volume of flow and resistance to flow. Usually the resistance to pulmonary flow is increased and the pulmonary arterioles and arteries exhibit structural changes (Edwards, 1957). Masee (1947) demonstrated occlusive intimal lesions of the pulmonary vessels in a patient who had pulmonary hypertension during life.

In patients who do not have pulmonary hypertension, the structure of the entire pulmonary tree is essentially normal, and the small arteries and arterioles have wide lumina and thin walls (Figure VI-17a, b). In the presence of moderate elevation of pulmonary pressure, the small muscular pulmonary arteries and arterioles show foci of fibrous intimal thickening which reduces the lumina (Figure VI-18c to f). Such lesions appear to result from excessive pulmonary flow. The non-obstructed pulmonary arteries and arterioles in patients with moderate pulmonary hypertension have wide lumina and often atrophic media with loss of the muscle. Patients with atrial septal defect whose pulmonary tension is elevated to a level approaching systemic pressure may show



Figure VI-17. Pulmonary vessels in adult patients with atrial septal defect. (From Edwards, 1957. Reproduced by permission of Grune & Stratton, Inc.)

a and *b*. From a woman 41 years old with high pulmonary flow and normal pressure in the pulmonary arteries. *a*. Small muscular artery and arteriolar branch, showing thin walls and wide lumina. (El-v-G. This abbreviation here and in subsequent legends indicates Verhoeff's elastic-tissue stain counterstained with van Gieson's connective-tissue stain.) X330. *b*. A large muscular artery and a bronchiole. The arterial wall is thin and the lumen is wide, features not distinguishable from the normal. El-v-G. X70.

c. From a patient 46 years old with left-to-right shunt and moderate pulmonary hypertension (pulmonary arterial pressure 89/20 to 100/37). Medial hypertrophy of large muscular artery, which lies beside a bronchiole. El-v-G. X70.

d, *e* and *f*. From a patient 34 years old with moderate pulmonary hypertension. *d*. A small muscular artery and an arteriolar branch with no related occlusive intimal lesions, showing exceedingly wide lumina. El-v-G. X200. The wall of the artery is atrophic, as illustrated in *f*. *e*. A small muscular artery and an arteriolar branch. Medial hypertrophy of artery and intimal occlusion by fibrous tissue of arteriolar origin. El-v-G. X330. *f*. Detail of wall in dilated artery shown in *e*. The medial muscle is almost entirely absent, the wall now being represented by the condensation of the two elastic laminae and fibrous thickening of the intima and adventitia. El-v-G. X570.



Figure VI-18 A large muscular artery showing intimal fibrous occlusion. (Hematoxylin and eosin, X 55.) Such lesions were widely distributed and in addition many foci of arterial necrosis were present in the lung. From a man with atrial septal defect, severe pulmonary hypertension and only a right-to-left shunt (From Edwards, 1957. Reproduced by permission of Grune & Stratton, Inc.)

occlusive intimal lesions in the large muscular arteries (Figure VI-18). These lesions may be identical with those seen in the end-stage of ventricular septal defect with pulmonary hypertension (page 306). Necrotizing arterial lesions may also be encountered in patients with severe pulmonary hypertension.

Pulmonary Embolism and Thrombosis. Occasionally atrial septal defect is associated with massive pulmonary emboli (Canada *et al.*, 1953), at other times, thrombi may develop on atheromatous lesions of large arteries (Taussig *et al.*, 1938). It may be thought that the obstructing emboli or thrombi cause the increased pulmonary vascular resistance but, in my opinion, this is not the usual way in which pulmonary hypertension is initiated in this anomaly. The earliest occlusive lesions of the arteriolar and small arteries should not be regarded as embolic or thrombotic in nature, the lesions seem merely to represent fibrous proliferation of the intima in response to trauma from high pulmonary flows. It is recog-

nized that thrombosis may follow pulmonary arteritis. The lesions are complications of pulmonary hypertension and the occluding thrombi accentuate but do not initiate the increased pulmonary vascular resistance.

Pulmonary Arterial Aneurysm. Deterling and Clagett (1947), in reviewing the literature, found that aneurysm of the pulmonary artery is caused by syphilis or is associated with an arteriovenous shunt. In the latter category, patent ductus arteriosus is the commonest underlying condition and atrial septal defect is relatively uncommon.

A number of cases of atrial septal defect with pulmonary arterial aneurysm have been reported (Wahl and Gard, 1931; Okkels and Therkelsen, 1932; Ravault *et al.*, 1947; Cunningham, 1948; Selzer and Lewis, 1949). Usually the pulmonary arterial aneurysm is identified clinically in patients with atrial septal defect, but in the case reported by Wahl and Gard (1931), the aneurysm was saccular and clinically was first thought to be a mediastinal tumor. Selzer and Lewis (1949) reported rupture of a pulmonary arterial aneurysm.

Paralysis of Left Vocal Cord. Rarely, in atrial septal defect, hoarseness may develop from paralysis of the left vocal cord as a result of compression of the left recurrent laryngeal nerve (Erlanger and Levine, 1943; Burrett and White, 1945).

Although the mechanism is still to be established, the existing evidence suggests that hoarseness of this type associated with atrial septal defect is a consequence of pulmonary hypertension. In the case reported by Wahl and Gard (1931), the left recurrent laryngeal nerve was compressed by a saccular aneurysm of the left pulmonary artery.

Valvular Disease. In the presence of an atrial septal defect any of the cardiac valves, except the aortic, may be the seat of concomitant complicating disease.

Mitral Stenosis (Lutembacher's Syndrome). The combination of atrial septal defect and mitral stenosis usually carries the designation, "Lutembacher's syndrome" (Figure VI-19). In this syndrome, the mitral stenosis may be regarded as a complication of atrial septal defect.

According to McGinn and White (1933) who made a comprehensive review of the literature, Martineau in 1865 was the first to report an example of this condition. Abbott's case was described in 1915, while Lutembacher's original report was made in 1916. McGinn and White analyzed 24 cases, and found a distinct predilection for the female sex. Gibson and Roos (1935) stated that in 22 of their 27 analyzed examples of Lutembacher's syndrome the sex was female. The predilection of this complex for the female sex, in all probability, is related to the tendency for mitral stenosis of rheumatic origin to be more common in females.

In the 24 cases reviewed by McGinn and White, 11 patients died before the age of 30, one patient lived to 74. The average age at death was 35 years. According to these authors, this is somewhat less than the average age at death of patients with mitral stenosis alone or of patients with uncomplicated atrial septal defect. Gibson and Roos (1935) stated that their patient with Lutembacher's syndrome, a boy aged 10 years, was the youngest reported to have died from this condition. They stated that Donnelly's patient, who died at the age of 2½ days, should not be classified as an example of Lutembacher's syndrome, since the patency of the foramen ovale was incidental. In that case (see Congenital Mitral Stenosis, page 388), the mitral stenosis was believed to have been of congenital origin.

In Lutembacher's syndrome the mitral stenosis is usually rheumatic and less commonly congenital (Soulié and associates, 1954). Although Lutembacher (1916) thought that the mitral stenosis in his patient, a woman aged 61 years, was congenital, it is possible that the stenosis was rheumatic. The atrial septal defect usually takes the form of a patent foramen ovale; this occurred in 18 of the 24 cases reviewed by McGinn and White.

In recent years the term "Lutembacher's syndrome" has fired the imagination of workers, with the result that more cases of this condition have been reported than probably exist. If the term is to retain a specific connotation, caution must be exercised in making this diagnosis. The existence of an atrial septal defect of sufficient size to be significant must be established, and evidence of stenosis of the mitral orifice must be incontrovertible (Nadas and Alimurung, 1952).

Cahen and associates (1952) indicated that, in cases of persistent common atrioventricular canal, the clinical diagnosis of Lutembacher's syndrome may be erroneous. Abbott (1915) published data

on comparable cases showing that, in patients with atrial septal defect, cardiac enlargement and pulmonary arterial dilatation were greater in degree if mitral stenosis was present than if mitral stenosis was absent. On the other hand, Gibson and Roos (1935) reported that in their 2 cases of atrial septal defect, 1 with and 1 without mitral stenosis, both hearts showed essentially the same degree of secondary effects. In some cases of atrial septal defect without associated mitral stenosis, enlargement of the right side of the heart and of the pulmonary trunk is as great as that found in cases of Lutembacher's syndrome.

Only 3 of the hearts with atrial septal defect, in the pathologic collection of the Mayo Clinic, had associated mitral stenosis. Cosby and Griffith (1949) found no examples of the syndrome among 19 cases of atrial septal defect studied at necropsy. Among 45 hearts with atrial septal defect obtained from 4 Boston hospitals, Gelfman and Levine (1942) found coexisting rheumatic disease in 5; only 2 of these were thought to be examples of true Lutembacher's syndrome.

Bacterial endocarditis. Bacterial endocarditis is a rare complication of the usual variety of atrial septal defect. When it occurs, the involvement is almost always on a valve



Figure VI-19. Lutembacher's syndrome in a man 51 years of age. The heart is viewed from the left, showing the large atrial septal defect and the rheumatic mitral stenosis. (From Edwards, J. E.: *Postgrad. Med.*, 3:327-341, 1918. Reproduced by permission of *Postgraduate Medicine*.)

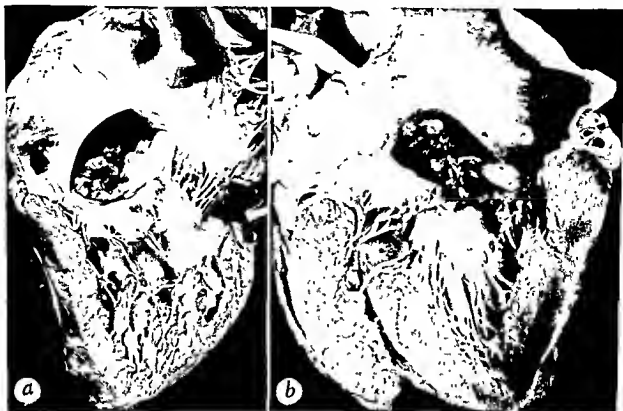


Figure VI-20 Subacute bacterial endocarditis complicating the partial variety of persistent common atrioventricular canal in a man 36 years old.

a. Viewed from the right, the inferior part of the atrial septum shows a defect immediately above an essentially normal tricuspid valve. Vegetations in the left side of the heart are seen through the atrial septal defect. The region of the foramen ovale is normally formed. The right ventricle is hypertrophied. (From Tinney and Barues, 1942. Reproduced by permission of the authors and *Minnesota Medicine*.)

b. Left side of heart. The defect in the inferior part of the atrial septum and the cleft in the mitral valve are indicative of the partial variety of the malformation. In addition, vegetations of subacute bacterial endocarditis are deposited on the anomalous valve. (From Rogers and Edwards, 1948. Reproduced by permission of C. V. Mosby Company.)

rather than on the edges of the defect. If one accepts the view that bacterial endocarditis is usually on a traumatic basis, this localization is explained by the low pressures in the atria and the large size of the defect which do not subject the edges of the defect to any particular stress. The rare occurrence of bacterial endocarditis in atrial septal defect agrees with the observations of Lillehei and associates (1953) who created atrial septal defects in dogs and then injected bacteria intravenously, but failed to produce bacterial endocarditis.

Among 45 patients with atrial septal defect, all of whom were more than 2 years of age, Gelfman and Levine (1942) found no instance of bacterial endocarditis. Jacobius and Moore (1938) men-

tioned a case of patent foramen ovale in which lesions of subacute bacterial endocarditis were present on the limbus of the fossa ovalis and on the mitral valve. Among 19 cases of fatal atrial septal defect, Cosby and Griffith (1949) encountered 1 case of bacterial endocarditis and stated that it did not involve the margins of the defect. In the case of Kurz and Fischer (1949), the mitral valve was involved by the subacute bacterial endocarditis. In 1 of the cases of Bedford and associates (1941), the bacterial endocarditis was on the wall of the left atrium. It did not involve the mitral valve nor presumably the margins of the atrial septal defect. The patient of Geiger and Anderson (1947), a woman of 55, had an atrial septal defect measuring 3.0 cm. in diameter. Bacterial endocarditis involved the anterior leaflet of the mitral valve but not the margins of the septal defect. Pulmonary infarcts were present,

apparently as a result of paradoxical embolism of vegetations from the mitral valve.

Although bacterial endocarditis is rare, it is more likely to occur in persistent common atrioventricular canal and in defects of the lower part of the atrial septum than in the usual variety of atrial septal defect. Among 56 cases of atrial septal defect involving the lower part of the atrial septum with associated atrioventricular valvular malformations, Rogers and I (1948) found 3 cases in which bacterial endocarditis involved the margins of the defect or the neighboring valves or both (Figure VI-20). Perhaps the infrequency of this complication is explained by death at an early age of many of the patients, and consequently, by the relatively small opportunity of bacteremia to cause such an infection. In the Mayo Clinic pathologic collection, 2 hearts with the usual variety of atrial septal defect had associated mitral valvular disease, believed to represent healed bacterial endocarditis.

Mitral insufficiency and tricuspid insufficiency. Atrial septal defects, which are part of persistent common atrioventricular canal, may have varying degrees of insufficiency of the mitral valve, tricuspid valve or both. In the partial variety, the concomitant cleft in the anterior leaflet of the mitral valve may make the latter incompetent. In the complete variety, the common atrioventricular valve may be incompetent.

Among cases of persistent common atrioventricular canal without atrial septal defect, insufficiency of either the mitral valve or tricuspid valve may develop. Under these circumstances, mitral insufficiency in my experience has been a consequence of healed bacterial endocarditis. Tricuspid insufficiency may complicate dilatation of the right ventricle that results from a large left-to-right shunt, coupled perhaps with right ventricular failure. The tricuspid valve is basically normal but its orifice becomes so large that the valvular tissue is inadequate to close it completely. The tricuspid or mitral insufficiency is associated with significantly elevated atrial pressure, a condition also present in Lutembacher's syndrome.

Pulmonary stenosis or insufficiency. The clinical physiologist, when performing cardiac catheterization on patients with atrial septal defect, commonly observes small gradients of pressure between the right ventricle and the pulmonary trunk. It has been thought that these gradients indicate mild or relative pulmonary stenosis. Al-

though the pulmonary valve is slightly dilated, it is not as wide as either the right ventricle or the pulmonary trunk and, in the presence of a large left-to-right shunt, it is responsible for a minor gradient of pressure in the absence of organic pulmonary stenosis (Weidman *et al.*, 1957). When pulmonary hypertension is present, the pulmonary cusps are stretched, with resulting fibrosis, varying degrees of retraction (Figure VI-21), and ensuing pulmonary valvular insufficiency. Available evidence suggests that pulmonary insufficiency in atrial septal defect is usually the result of pulmonary hypertension (Barber *et al.*, 1950, Leatham and Gray, 1956) and cannot be demonstrated in patients with normal pulmonary arterial pressures.

Cerebral Abscess. Cerebral abscess, although a relatively common complication of congenital cardiac disease, is rather uncommon in atrial septal defect (Tyler and Clark, 1957).

Maronde (1950) found at necropsy 1 instance among 59 cases of atrial septal defect not asso-



Figure VI-21. Pulmonary trunk and ascending aorta, from a woman 48 years old with atrial septal defect and pulmonary hypertension. The pulmonary trunk (lower portion of illustration) is considerably wider than the aorta. The cusps of the pulmonary valve are thickened and retracted by fibrous tissue. The available evidence suggests that the pulmonary valve had been incompetent.

ciated with other malformations. Sancetta and Zimmerman (1950), in a review of the literature, encountered 44 cases of cerebral abscess complicating congenital cardiac disease; 3 of these had defects of the atrial septum without associated malformations. In the pathologic collection of the Mayo Clinic, cerebral abscess (Gates *et al.*, 1947) was present in 2 of the 44 cases of atrial septal defect exclusive of the cases subclassified as persistent common atrioventricular canal. In both cases, the atrial septal defect was of the usual type.

Significant Right-to-Left Shunt; Cyanosis. In uncomplicated atrial septal defect a right-to-left shunt may occur, but is of small proportion, and its presence usually can be determined only by dye-dilution techniques; cyanosis is not present. In some complicated cases however, a significant right-to-left shunt occurs, and with it cyanosis may appear. This late appearance of cyanosis has been termed *cyanose tardive*. Bard and Curtillet (1889) are credited with having introduced this term which Maude Abbott (1915) later used as a basis of classification of congenital heart disease.

The two commonest ultimate causes of significant right-to-left shunt are right ventricular failure with elevation of right ventricular diastolic pressure, and pulmonary hypertension. The latter may be responsible for a significant right-to-left shunt by virtue of increased thickness of the muscle of the right ventricle which may approach that of the left ventricle. Elements of right ventricular failure also may contribute to the increased resistance to filling in instances of pulmonary hypertension.

In 1949, Selzer and Lewis reviewed 180 cases of atrial septal defect from the literature and found evidence of chronic cyanosis in 11. One of the patients with cyanosis was a 35-year-old man who also had a pulmonary arterial aneurysm. Dexter (1956), confirming the findings of Limón Lason and Alvarez (1949) and of Soulié and associates (1954), observed that in patients with atrial septal defect who had significant desaturation of the brachial arterial blood, the pulmonary venous blood was normally saturated. From such observations, Selzer and Lewis, and Dexter stated that diffusion of oxygen across the alveolar membrane is not abnormal in these patients, even in the presence of severe pulmonary vascular dis-

ease. The desaturation of the systemic blood is dependent on a right-to-left shunt, a feature which is readily demonstrable by dye-dilution techniques (Swan *et al.*, 1953; Swan *et al.*, 1954).

In most patients with atrial septal defect and a significant right-to-left shunt, the presence of a significant left-to-right shunt usually is also readily demonstrated. In rare instances, the demonstrable shunt is entirely in a right-to-left direction (Shepherd *et al.*, 1957). Cyanosis, in association with atrial septal defect, usually represents a complication (Selzer and Lewis); it had been present since birth in only 2 of the 11 cases which they found in the literature. In the majority of the others it appeared in the second decade of life.

Paradoxical Embolism. Paradoxical embolism usually concerns the spread of emboli from the right circulation across an abnormal opening into the left circulation. Rarely paradoxical flow may be from the left side into the lesser circulation. Usually paradoxical embolism is a manifestation of the right-to-left shunt across the atrial septum but, in rare instances, it may be across a ventricular septal defect or even through a patent ductus arteriosus. For practical purposes, paradoxical embolism is encountered more commonly in valvular-competent, patent foramen ovale than in true atrial septal defect, because the former defect is so much commoner. It is probable, however, that the incidence of paradoxical embolism is lower among patients with patent foramen ovale than among those with true atrial septal defect (Beattie, 1925).

The historical aspects of paradoxical embolism have been reviewed by several authors (Abbott *et al.*, 1923; Thompson and Evans, 1930; Hirschboeck, 1935; Ingham, 1938; Young *et al.*, 1948).

As a rule, the occurrence of paradoxical embolism by way of a valvular-competent, patent foramen ovale, is preceded by significant pulmonary embolism. Subsequent pulmonary embolism produces increased pulmonary pressure and is responsible for a right-to-left shunt. In true atrial septal defect, paradoxical embolism may occur in the absence of pulmonary emboli since a right-to-left shunt of some degree usually exists.

Paradoxical emboli tend to reach the cere-

bral vessels. As a rule, the paradoxical embolism is composed of bland thrombotic material, but it may contain tumor tissue or infected material. Thompson and Evans (1930) emphasized that, when paradoxical embolism of either tumor tissue or bacteria is suspected, one must consider the possibility of spread of the tumor or infectious process from the lungs by way of the pulmonary veins to the left side of the heart.

Cardiac Failure. Cardiac failure in atrial septal defect is usually predominantly right ventricular. Dexter (1956) reviewed this problem and indicated that failure of the right ventricle is dependent basically on the amount of work required of the right ventricle. Factors that lead to increased work of the right ventricle are: (1) increase in its output, (2) increase in pressure that it exerts in cases of pulmonary hypertension, and (3) possible occurrence of tricuspid insufficiency in the presence of a dilated right ventricle. Left ventricular failure is said to occur occasionally in patients with atrial septal defect.

In the complete type of persistent common atrioventricular canal, subvalvular interventricular communications are common. The resultant dynamics are those of large ventricular septal defect and incompetence of the mitral and tricuspid valves, in addition to those of interatrial communication. Failure of both ventricles is probably the explanation for early death of patients with this type of malformation.

CAUSES OF DEATH

In 1954, Braudo and associates reviewed the causes of death in 80 patients with atrial septal defect. In only 35 was death related to the malformation, and in 25 of these, congestive heart failure was the responsible cause.

Heart failure in atrial septal defect may simply be related to the effects of the large left-to-right shunt, but in many instances the complicating features, either pulmonary hypertension or atrioventricular valvular disease, are additional precipitating factors. Less common causes of death in atrial septal defect include embolism (either pulmonary or paradoxical), pulmonary thrombosis (Canada *et al.*, 1953), subacute bacterial endocarditis, abscess of brain (Sancetta and Zimmerman, 1950; Maronde, 1950), paroxysmal tachycardia (Dry, 1948), and rupture of a pulmonary arterial aneurysm (Selzer and Lewis, 1949).

SURGICAL CORRECTION

The surgical techniques and their indications are discussed in Chapter XVII.

DEVELOPMENTAL BASIS

The developmental basis for the various types of atrial septal defect is discussed in Chapter II (page 46).

Defects at Fossa Ovalis. The commonest defects of the atrial septum, those at the fossa ovalis, represent incompetence of the valvular mechanism of the foramen ovale. Defects of this type may be the result of any one or of a combination of the following conditions: (1) a short valve of the foramen ovale or overresorption of the septum primum, (2) a perforation of the valve of the foramen ovale or ectopic resorption of the septum primum, or (3) an excessively large foramen ovale with normal development of the valve of the foramen. The last condition may represent a deficiency in growth of the septum secundum.

Defects in Lowermost Portion of Atrial Septum (Persistent Common Atrioventricular Canal). Defects of the atrial septum, which are part of the complex of persistent common atrioventricular canal, developmentally are intimately related to failure of normal partitioning of the embryonic common atrioventricular canal. Deficiencies in the growth of the atrioventricular endocardial cushions result in incomplete formation of either the tricuspid or mitral valve or of both valves, which is represented grossly by a cleft in the involved valve or valves. Failure of the septum primum and the septum secundum to fuse with the atrioventricular endocardial cushions is the basis for the atrial septal component of this anomalous complex. Although the older literature indicated that the deficiency is entirely of the septum primum, Wakai and Edwards (1956) have suggested that this component of the complex may result from a deficiency in upward growth of the atrioventricular endocardial cushions alone or as part of a deficiency of both the septum primum and the septum secundum. The interventricular communication that is present frequently in the complete variety of persistent common atrio-

ventricular canal may be explained by deficiency in the downward growth of the atrioventricular endocardial cushions; this results in incomplete fusion of the muscular portion of the ventricular septum with the undersurfaces of the atrioventricular valves. Likewise, failure of downward growth of the atrioventricular endocardial cushions is responsible for the deficiency in the membranous portion of the ventricular septum which often characterizes the heart with persistent common atrioventricular canal.

Defects in Uppermost Portion of Atrial Septum. The developmental basis for the defect that lies superior to the fossa ovalis has been explained (Hudson, 1955; Edwards and Helmholz, 1956; Swan *et al.*, 1957) as an anomalous connection of the pulmonary veins. The rea-

soning is that, when an anomalous connection between the pulmonary venous system and the superior vena cava is maintained, the gradual growth of the heart will result in a defect which appears to be of the atrial septum. In reality, the defect lies above the true atrial septum.

Ross (1956) suggested a somewhat similar basis for this defect. He explained that, in normal development, the direct connection between the pulmonary veins and the heart takes place between the pulmonary veins, on one hand, and the portion of the sinus venosus that will become left atrium, on the other. If the pulmonary veins initially connect to the part of the sinus venosus that will become the right atrium, the connection of the pulmonary veins will be anomalous and will result in a defect of this type.

PREMATURE CLOSURE OF FORAMEN OVALE

Early workers, concerned largely with the structure of the fetal heart, concluded that practically the entire stream of inferior caval blood passed through the foramen ovale to the left atrium. Later studies (Barclay *et al.*, 1944; Barron, 1944; Barcroft, 1947) have indicated that, although a substantial proportion of the inferior caval blood follows this route, some of it enters the right atrium and mingles there with the blood entering from the superior vena cava. If we omit from consideration the still controversial matter of the proportion of the inferior caval current that passes directly to the left atrium, it is clear that the left side of the fetal heart must receive a considerable proportion of its intake by way of the valvular mechanism at the foramen ovale. This shunt is obviously a necessary mechanism for maintenance of the right-left balance in the prenatal development of the heart and for its normal postnatal functioning.

The appearance of the atrial septum may vary in premature closure of the foramen ovale. The septum may show a properly formed foramen ovale but the opening may be closed by a membrane. This condition may be interpreted as fusion of the valve of the foramen ovale with the interatrial septum secundum. The foramen ovale

may be absent; that is, the septum secundum appears to have grown beyond its normal bounds, leaving no opening (foramen ovale). In still other cases, a narrow slitlike opening may be noted at the foramen ovale (Wilson *et al.*, 1953; Gresham, 1956), and associated changes reflect the absence of normal filling of the left side of the heart during fetal life and the concomitant overburdening of the right side of the heart. Thus, the chambers of the left atrium and ventricle are noticeably smaller than normal and the cardiac chambers on the right side are larger than normal. The right ventricular wall is hypertrophied and the ductus arteriosus is unusually wide.

Normally in the fetus the left atrium receives blood from two sources: (1) from the lungs by way of the pulmonary veins and (2) from the right atrium through the foramen ovale. The development to normal size of the left cardiac chambers seems dependent on blood entering the left atrium from both these routes. If the foramen ovale closes during fetal life, the left atrium receives blood only from the pulmonary veins. The volume received is evidently insufficient to cause the left cardiac chambers to develop to their normal capacities. As will be explained later, this underdevelopment is probably the basis for some of the postnatal functional disturbances resulting from premature closure of the foramen ovale.

More directly related to fetal well-being is the burden that this condition places on the right side of the heart. This portion of the heart attempts to

accommodate to the greater volume of blood that it must carry, but *right ventricular failure* may develop during fetal life. When this happens, the fetus shows the same signs of chronic cardiac failure that are seen in congestive failure during post-natal life. Hydramnion may be associated.

If cardiac failure develops during fetal life, stillbirth may result or the infant may be born alive but be severely edematous (Benner, 1939). The infant may appear normal at birth but develop cyanosis in the neonatal period. This manifestation may be the result of underdevelopment of the left atrium and ventricle, and may be explained as follows: When the left side of the heart is smaller than normal, it may not be able to receive a normal amount of blood, leading to increased pressure within the pulmonary vessels. If this pressure exceeds that within the aorta and if the ductus arteriosus remains open, venous blood will be shunted into the aorta. On the other hand, if the ductus closes, difficulty may be caused by progressive elevation in pulmonary capillary pressure resulting from inability of the pulmonary veins to empty properly, coupled with constant forcing by the right ventricle of more blood into the lungs. Under such conditions, life soon fails from pulmonary edema.

Wilson and associates (1953) reported on 17 cases of premature closure of foramen ovale, in

some of which the foramen ovale was atretic, in others stenotic (less than 5 mm. in diameter). None of the patients lived more than 5 weeks and only 5 of the 17 lived more than 1 day.

The *developmental basis* for premature closure of the foramen ovale has already been suggested (Chapter II). Theoretically it may arise in two different ways: (1) The septum secundum may overgrow to such an extent that no foramen ovale is left (Lehman, 1927; Patten, 1938; Wilson *et al.*, 1953, Case 1; Brody, 1953, Case 1; see Figure VI-22). Patten has pointed out that this malformation is a result of local overgrowth rather than of developmental arrest. (2) Premature closure might result if, after normal formation of the atrial septal complex, the valve of the foramen ovale becomes fused to the septum secundum, as it does in the majority of persons some time after birth.

A similar phenomenon might be seen in the heart of the newborn infant in whom the tract from the foramen ovale into the left atrium is present but narrower than normal (Benner, 1939, Case 2; Read and Krumbhaar, 1932; Wilson *et al.*, 1953, Case 2, Gresham, 1956). Gresham

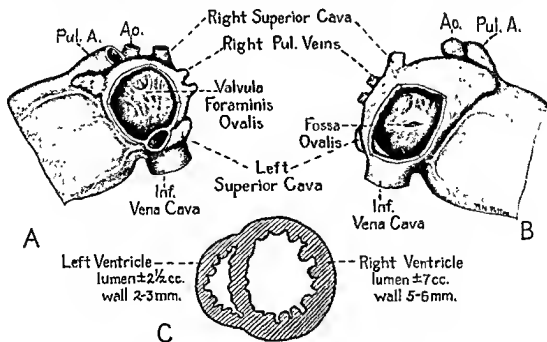


Figure VI-22. Premature closure of foramen ovale in an infant. (From Patten, 1938. Reproduced by permission of the author and *American Journal of Pathology*.) A. The valve of the foramen ovale is adherent to the septum. B. The fossa ovalis is represented as a small slit. C. The large right ventricle and the small left ventricle are the consequence of lack of trans-atrial flow in the fetus.



Figure VI-23. Aneurysm of fossa ovalis from diabetic woman 55 years old who died of congestive heart failure resulting from extensive myocardial infarction. *a.* Right atrium. Note aneurysm at the fossa ovalis. The probe has passed through a valvular-competent, patent foramen ovale and disappeared in the left atrium. *b.* Left atrium. The probe has passed through the valvular-competent, patent foramen ovale and appears in the left atrium. The aneurysm of the fossa bulges into the left atrium.

noted fibrous endocardial thickening of the left atrium and ventricle in his case and suggested that the ventricular change resulted from primary premature closure of the foramen ovale which had prevented highly oxygenated placental blood from entering the left chambers of the heart. An alternate explanation is that primary endocardial sclerosis existed and that premature closure of the foramen ovale was a secondary phenomenon. Gresham stated that all previously reported cases had left ventricular endocardial thickening.

Raeburn (1951) thought that pressure from a diaphragmatic hernia was responsible for premature closure of the foramen ovale in his patient. Brody (1953) reviewed 11 cases, including 2 of his own. Four were taken from the literature of the last century. He noted associated major cardiac anomalies in 2 of the 11. In the case of Vernon, a newborn that lived 4½ hours, both the aorta and the pulmonary trunk arose from the right ventricle and a ventricular septal defect was present. In the second case (Brody's Case 2), a newborn that lived 36 hours, persistent truncus arteriosus and ventricular septal defect were also present.

I have examined the heart of a newborn that

lived 10 hours, with premature closure of the foramen ovale, ventricular septal defect and coarctation of the aorta.

Whatever the cause of the valvular deformity, whether developmental or inflammatory, its presence in the neonatal period means that it had developed during fetal life. With valvular stenosis present, it is conceivable that the left atrial pressure during fetal life might have been greater than normal and possibly greater than the right atrial pressure. Such a condition would be similar to postnatal atrial pressure relationships, for in fetal life, as after birth, there would be a tendency for the valve of the foramen ovale to be pressed against the interatrial septum secundum and to fuse with this component of the atrial septal complex.

Similar explanations are applicable to the case of Edwards and DuShane (1950) in which congenital mitral atresia was associated with premature closure of the foramen ovale (see Congenital Mitral Atresia, page 386).

ANEURYSM AT FOSSA OVALIS

Occasionally the floor of the fossa ovalis (septum primum) bulges into either the right or the left atrial chamber (Lang and Posselt,

1934). When this happens, the foramen ovale is usually, but not always, closed and the bulge results because the floor of the fossa

is redundant and the pressure is greater in one atrium than in the other (Figure VI-23). Under ordinary circumstances the bulge would be toward the right, since normally the left atrial pressure exceeds the right atrial pressure. Cases such as Canavan's (1940), in which the aneurysm bulged into the left atrium, have been explained on the basis of

cardiac failure, which in turn resulted in elevation of right atrial pressure.

I have observed 6 instances of aneurysm of the fossa ovalis, 3 were in adults, 1 was in a newborn infant with tricuspid atresia, and the other 2 were in children. Each of the latter had a large ventricular septal defect and the aneurysm protruded into the right atrium.

REMNANTS OF VALVES OF SINUS VENOSUS: CHIARI'S NETWORK

The right atrium of many normal hearts contains remnants of the valves of the sinus venosus. It may be recalled that, as the developing sinus venosus is incorporated into the wall of the right atrium, the valve leaflets of the sinus venosus (the *valvulae venosae*) project into the right atrial chamber. The right valve normally develops into the valve of the inferior vena cava (eustachian valve) and the valve of the coronary sinus (thebesian valve). This evolution of two valves from one involves a considerable reduction in extent and a division into two components of the remnants of the right *valvula venosa*. Normally the left valve suffers even greater reduction and its remnants blend with the septum secundum of the interatrial septal complex. Yater (1929) reviewed the literature on the fate of the *valvulae venosae* and reported on a study of a large number of hearts of adults from the point of view of identifying structures related to these valves. Most of the comments that follow are taken from his comprehensive and excellent review. In a series of hearts he was able to find a variety of changes illustrating gradual progression from unusually large but structurally normal thebesian and eustachian valves to those which showed features resulting from embryologic deviation.

In 16 of a series of 120 hearts, Yater (1929) found that, except for the thebesian valve, a ridge was all that indicated the previous existence of the right valve. In 69 cases the valve of the inferior vena cava was crescentic. In some cases this crescentic valve was thin, transparent and distinct from the margin of the inferior vena cava. In other cases it was firm and merged with the rim of the inferior vena cava and the wall of the

atrium. In 22 cases, he found a fenestrated semilunar membrane containing one or several small openings. In most of these cases the valve was thin. In 7 cases the valve of the inferior vena cava was formed in part or entirely by a network of fibers resembling a cobweb. In all the foregoing cases, the valve of the inferior vena cava and that of the coronary sinus were distinct from each other. In 2 of Yater's 120 cases, both valves were formed of one membrane. Three hearts had a Chiari's network.

It is evident that the formation of the valves of the inferior vena cava and coronary sinus always entails a considerable reduction in the primitive right valve of the sinus venosus from which they are molded. In many instances this reduction is so great that these valves are scarcely more than vestigial folds.



Figure VI-24. Chiari's network. Right atrium. One band of the network (right upper part of figure) is attached to the crista terminalis near the mouth of the superior vena cava. From a woman 74 years of age.



Figure VI-25 Chiari's network. From a man 69 years old (Drawing by Louise Horne, Wayne County General Hospital, WCGH, 45-A 354)

Not infrequently the resorptive process, by which the valves are shaped, results in fenestration which in some instances may be so extensive that the valvular tissue is represented only by delicate threadlike strands. According to Yater, in keeping with Chiari's (1897) original description, the mere presence of fenestrated valves should not be called Chiari's network. In all of Chiari's cases, some of the fibers of the network had some attachment either to the atrial wall near the upper portion of the crista terminalis or to the atrial septum. Therefore, the term "Chiari's network" probably should be applied only to reticular formations which possess threads with such widespread attachments. Thus, *Chiari's network* may be defined as a network of fine or coarse fibers in the right atrium with attachments extending from the region of the crista terminalis to the valves of the inferior vena cava and coronary sinus, or even to the floor of the right atrium in the region of the orifice of the coronary sinus (Figures VI-24 and VI-25).

Wright and his associates (1948) examined 512 hearts in the anatomic dissecting room. In 9 they found fibrous cords attached to the free edge of the valve of the inferior vena cava; in 8 of these the opposite extremities of the cords were attached to the atrial wall but not to the crista terminalis; in the ninth case the cords were attached to the crista terminalis. In keeping with the tenets of Yater, Wright and his associates expressed the opinion that Chiari's network was present only in the last case cited.

Functionally Chiari's network is probably of no importance usually. Several reported cases mentioned in Yater's review were instances of pulmonary embolism in which thrombotic material was attached to the network. In most of these cases thrombi were also present in the veins of the inferior extremities. To interpret the foreign material in the valve membrane as an embolus caught in the network, rather than as a thrombus starting at this point, seems plausible. In one of his cases, Chiari (1897) thought that pulmonary embolism had resulted from thrombi originating in the network. Rossall and Caldwell (1957) described a case in which an unusually large valve of the inferior vena cava had evidently caused significant obstruction to flow of blood.

Remnants of the left valvulae venosae are



Figure VI-26. Remnants of left sinus venosus attached to septum secundum and posterior portion of fossa ovalis.

frequently present in normal hearts. These are represented by a reticulum of fibers, at times resembling chordae tendineae, attached to the right side of the atrial septum in the region of the posterior half of the fossa ovalis. As a rule, these flattened cords or bands do not lie free but are intimately attached to the atrial septum (Figure VI-26). In rare cases, portions of the filaments may extend freely into the right atrial chamber or, also in rare cases such as that of Swan (1898-99), a membrane may be attached to the posterior portion of the fossa ovalis and extend as a valve flap into the right atrial chamber. Although Swan

thought that the heart in his reported case had a Chiari network, Yater's interpretation that it represents remnants of the left valve of the sinus venosus seems to be correct. Remnants of the left valve of the sinus venosus are usually of no functional consequence.

According to Yater, Przewoski in 1896 described networks of fibers in the right atrium near the mouth of the great veins and along the limbus of the fossa ovalis. He expressed the belief that the networks represented remnants of the venous valves of the embryo. This interpretation antedated by a year Chiari's more exact descriptions and interpretations.

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Congenital Malformations

B. Malformations of the Ventricular Septal Complex

JESSE E. EDWARDS

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General Considerations

IN THE FEW years since the writing of the first edition of this chapter the following major principles have evolved concerning ventricular septal defects:

1. Ventricular septal defect exhibits a wide spectrum of behavior. Some patients with this defect are asymptomatic; others suffer from left ventricular failure in infancy or childhood, without cyanosis; and still others become cyanotic in the later stages of this disease, usually in adolescence or early adult life.

2. The idea has been championed (Selzer, 1949; 1954a and b) that in ventricular septal

defect the behavior of the circulation depends, not principally on the position of the defect, but rather on its size (Figure VI-27). Two major forms may be designated as the "large" and the "small." The diameter of a large defect is about as large as that of the orifice of the aortic valve, whereas a small defect is significantly smaller.

3. Small defects are obstructive and allow a normal differential in pressure to be built up between the lesser and greater circulations (Selzer, 1954a; Blount *et al.*, 1955; Figure VI-27a).

4. Large defects allow free communication between the ventricles, and the functional result is the same as though a single ventricle

existed. No essential differential in pressure is present between the two ventricles, and pulmonary hypertension exists (Dexter *et al.*, 1950, Blount *et al.*, 1955).

5. In large defects, the direction of the shunt or shunts depends on the resistance to pulmonary flow as compared to the resistance to systemic flow (Figure VI-27*b, c*) (Burchell and Wood, 1948, Hamilton *et al.*, 1950, Selzer and Laqueur, 1951, Dammann and Muller, 1953; Edwards, 1957). The position of the defect is not a primary factor in determining whether a right-to-left shunt occurs. In the majority of patients with ventricular septal defects the aorta is in direct connection with the right ventricle, but if a large ventricular septal defect is remote from the aortic orifice, *e.g.*, near the apex, the dynamics may be like those in large ventricular septal defects located near the aorta (Neill, 1951; Heath *et al.*, 1956).

6. Abbott's suggestion (1927) that ventricular septal defect in an adult with cyanosis (described by Eisenmenger in 1897) represents an entity of a specific cardiac malformation cannot be supported (Selzer and Laqueur, 1951; Blount *et al.*, 1955, Edwards, 1957). It is now thought best to eliminate the

term "Eisenmenger's complex" from classifications of cardiac malformations. The right-to-left shunt associated with that term is not an expression of the anatomic peculiarities of the heart but rather, of high pulmonary vascular resistance in the presence of a "large" ventricular septal defect, regardless of its position. When reference is made herein to the term "Eisenmenger complex," the author will assume that it refers to a large ventricular septal defect with pulmonary hypertension and, in most cases, a right-to-left shunt.

7. In ventricular septal defect and pulmonary (or subpulmonary) stenosis the magnitude and direction of shunt or shunts depend, not principally on the relations of the great vessels to the defect but rather, on the degree of obstruction to pulmonary flow compared with resistance to systemic blood flow (Burchell and Wood, 1948; Hamilton *et al.*, 1950, Selzer and Carnes, 1953; Blount *et al.*, 1955; Edwards, 1957).

In ventricular septal defect with pulmonary stenosis, the degree of stenosis varies and so does the behavior of the cardiovascular system. Thus, in mild pulmonary stenosis, the functional picture may be indistinguishable from that in large ventricular septal defect

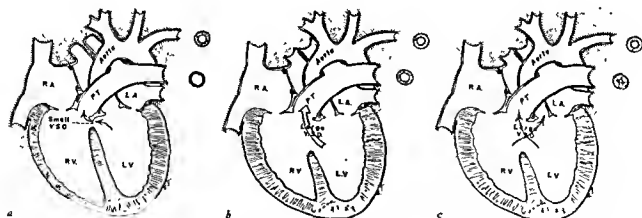


Figure VI-27. Intracardiac circulation in small and large ventricular septal defects. The circles beside each diagram indicate the relative resistance to systemic flow (upper circle) and to pulmonary flow (lower circle). (From Edwards, 1957. Reproduced by permission of Grune & Stratton, Inc.)

a. Small ventricular septal defect. The pulmonary resistance is relatively normal, bearing essentially normal relationship to the systemic resistance. The shunt is from left to right, the right ventricular wall is not hypertrophied. b. Large ventricular septal defect with pulmonary resistance greater than normal but slightly lower than systemic resistance. The shunt is from left to right. The pressure in both ventricles is essentially the same, and the right ventricular wall is hypertrophied. c. Large ventricular septal defect with pulmonary resistance considerably higher than systemic resistance. Here the shunt is from right to left. A left-to-right shunt also may be present, but frequently at this stage of the disease it is of minor nature.

without pulmonary stenosis. In such patients no right-to-left shunt exists. At the other end of the scale are hearts with essentially the same structural abnormalities but with associated severe pulmonary stenosis; such patients have a large right-to-left shunt and clinically represent classic examples of the tetralogy of Fallot. At the same time the functional changes are similar to those of patients with ventricular septal defect without pulmonary stenosis, in whom resistance to flow through the small pulmonary arterial vessels is extremely great.

It thus becomes apparent that, in different persons with the same anatomic malformation,

the functional pictures may be different (Edwards, 1950a).

In the first edition of this work, the tetralogy of Fallot was discussed under the malformations of the cono-truncal region. From a strict developmental point of view, such a classification is correct. In this edition, however, the subject is included in the present section on Malformations of the Ventricular Septal Complex. This is justified by the principles already listed, since among cases of ventricular septal defect with pulmonary stenosis the functional variations may be duplicated by instances of ventricular septal defect without obstruction to blood flow in the major arterial pathways to the lungs.

VENTRICULAR SEPTAL DEFECT WITHOUT PULMONARY STENOSIS

Applied Anatomy of Ventricular Septum

In order to define the pathologic anatomy of ventricular septal defects, it is essential to identify certain anatomic landmarks in the heart, especially in the outflow tracts of the ventricles where the majority of the defects occur (Becu *et al.*, 1956). From the right ventricular aspect the significant landmarks are: (1) tricuspid ring, (2) papillary muscle of conus, (3) crista supraventricularis, and (4) annulus fibrosus of pulmonary valve (Figure VI-28a). With the heart *in situ*, the tricuspid valve has the most inferior position of the four structures. The other three lie in progressively anterosuperior positions, in the order given.

The papillary muscle of the conus is a portion of the septal wall of the right ventricle into which chordae from the left half of the anterior tricuspid leaflet and the adjacent anterior half of the septal leaflet of the valve insert. At times, this structure is a well-formed papillary muscle, at other times, it is simply the region of the septum in which the aforementioned chordae attach. The crista supraventricularis is a ridge of muscle that originates at the tricuspid ring and arches upward toward the pulmonary valve along the septal wall of the outflow tract of the right ventricle. It should be emphasized that the uppermost portion of the right ventricular outflow tract lies at a more superior level in the body than does the aortic valve. The crista supraventricularis corre-

sponds to the same horizontal level in the body as the central portion of the right aortic sinus. It should also be pointed out that the entire aortic valve is not confined to the same horizontal level of the body. The left aortic cusp, near its junction with the right, lies most superiorly and corresponds in position to that of the left cusp of the pulmonary valve. The rest of the aortic valve lies more inferiorly in the body, the posterior cusp being most inferior.

With these considerations in mind, let us now examine the relations of the left ventricular aspect of the outflow portion of the ventricular septum. From the left ventricular aspect, the outflow portion of the ventricular septum lies immediately inferior to the aortic valve (Figure VI-28b). An imaginary line drawn through the center of the right aortic cusp corresponds to the tissue between the papillary muscle of the conus and the crista supraventricularis of the right side of the outflow portion of the ventricular septum. The membranous portion of the ventricular septum lies postero-inferior to the papillary muscle of the conus when viewed from the right side and is overhung by chordae which arise from the septal leaflet of the tricuspid valve. The left ventricular aspect of the membranous septum lies inferior to the commissure between the right and posterior aortic cusps and varied amounts of tissue under the corresponding valve cusps. Posterior to the membranous portion of the ventricular septum is the anterior leaflet of the mitral valve and the septal leaflet of the tricuspid valve. This relation-

ship is particularly striking when defects exist in this area, in which case the continuity of tissue of these two atrioventricular valves is readily apparent.

Normally the aorta is in close relationship with the right ventricle. Particular reference may be made to communication of the aorta with the right ventricle in the presence of a ventricular septal defect. The communication between the right ventricle and the aorta does not necessarily represent an abnormal position of the aorta. In the normal heart the ventricular septum prevents the aorta from communicating with the right ventricle; this becomes apparent if a portion of the ventricular septum immediately beneath the aortic valve is excised to create a simulated ventricular septal defect. The steps are illustrated in Figure VI-29

Pathologic Anatomy

Ventricular septal defects may be divided

into four groups as follows: (1) defects related to ventricular outflow tracts (Figure VI-30); (2) defects related to ventricular inflow tracts, (3) defects common to both inflow and outflow portions of ventricular septum, and (4) left ventricular-right atrial communications.

DEFECTS RELATED TO VENTRICULAR OUTFLOW TRACTS

Defects Posteroinferior to Crista Supraventricularis. The majority of ventricular septal defects involve the outflow portion of the ventricular septum and, of these, most but not all lie immediately posteroinferior to the crista supraventricularis (Figure VI-31). From the right side these defects are seen to lie in relation to the chordae which emanate from the papillary muscle of the conus. In some



Figure VI-28. Anatomic features of normal ventricular septum. (From Becu and associates, 1956. Reproduced with permission of Grune & Stratton, Inc.). *a*, Right ventricular aspect. The septal leaflet of the tricuspid valve (S.T.V.) demarcates the junction of the right atrium (R.A.) and the right ventricle. The septal leaflet of the tricuspid valve has been retracted upward to demonstrate the membranous portion of the ventricular septum (hatched circle). Anterior and superior to this is the papillary muscle of the conus (P.M.C.). From this muscle, chordae extend to the adjacent portions of the septal and anterior leaflets of the tricuspid valve. Anterosuperior to the papillary muscle of the conus lies the crista supraventricularis (C.S.). Anterosuperior to the latter lie the pulmonary valve and pulmonary trunk. P.T. indicates pulmonary trunk; R.P.L., right pulmonary cusp, L.P.L., left pulmonary cusp, P.R.V., posterior wall of right ventricle; A.R.V., anterior wall of right ventricle, and A.P.M., anterior papillary muscle of tricuspid valve. The dotted vertical line corresponds to the center of the right aortic cusp which lies at the other side of the heart illustrated in *b*. *b* Outflow tract of left ventricle and aorta. The membranous septum (M.) lies inferior to the commissure between the posterior (P.) and the right (R.) aortic cusps and beneath adjacent portions of the right and posterior aortic cusps. The membranous septum also lies anterior to and in contact with the anterior aspect of the anterior mitral leaflet (A.M.). The left aortic cusp (L.A.L.) has been sectioned in opening the aortic valve. P.M. indicates posterior mitral leaflet; A.L.V., anterior wall of left ventricle, L.C.A., ostium of left coronary artery; and P.T., pulmonary trunk.

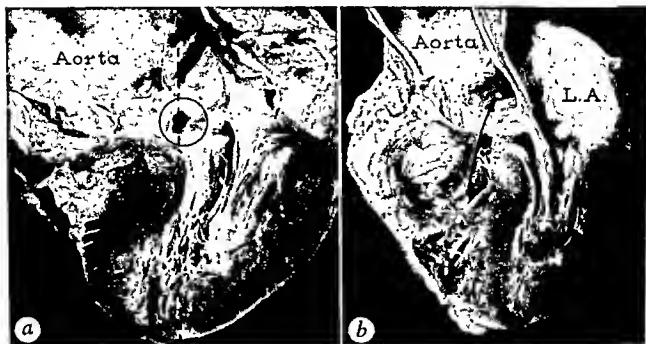


Figure VI-29 Normal heart in which ventricular septal defect was artificially created in pathologic specimen, defect lying in common location for naturally occurring ventricular septal defects. (From Edwards and associates, 1954. Reproduced by permission of Charles C Thomas.) *a*. The defect has been created inferior to the commissure between the right and posterior (unicus) aortic cusps (within circle). The dotted line indicates the plane of section that subsequently was made through the heart and which is illustrated in *b*. *b* Heart sectioned through aorta and artificially created ventricular septal defect, viewed from in front. The right ventricle now communicates readily with the aorta because of removal of the ventricular septum. This demonstration supports the concept that, in ventricular septal defects which occur in relation to the aortic valve, the communication between the aorta and the right ventricle is a natural consequence of the defect and does not depend on abnormal position of the aorta.

instances, the defect does not extend posteriorly beyond a line through the chordae which insert into the papillary muscle of the conus. In other instances, the defect extends beyond this line and involves in varying degree the membranous portion of the ventricular septum. Most defects which lie posteroinferior to the crista supraventricularis have the latter structure as their anterosuperior boundary; occasionally a defect is confined to the tissue posteroinferior to the chordae which insert into the papillary muscle of the conus. With respect to the left ventricular aspect, defects which lie posteroinferior to the crista supraventricularis on the right side are seen to lie inferior to the posterior half of the right aortic cusp, and if they extend to involve the membranous portion of the ventricular septum, they also lie inferior to the adjacent half of the posterior aortic cusp. This type of de-

fect has been generally classified in the past as a defect of the membranous portion of the ventricular septum.

Defects Anterosuperior to Crista Supraventricularis (Figure VI-32). A less common variety of ventricular septal defect lies above the crista supraventricularis. From the right ventricular aspect, such defects are seen to lie immediately beneath the pulmonary valve. From the left ventricular aspect, they lie inferior to the left aortic and adjacent half of the right aortic cusps. The membranous portion of the septum is intact. When defects involve the outflow portion of the ventricular septum, the aortic valve forms one boundary of the defect, and the right ventricle communicates with the aorta. At times, the close relationship between the right ventricle and the aorta has been referred to as "dextro-position of aorta," but the implication that

the position of the aorta is abnormal is not justified (Eisenmenger, 1898; Selzer and Laqueur, 1951; Edwards *et al.*, 1954).

DEFECTS RELATED TO INFLOW PORTION OF VENTRICULAR SEPTUM

Defects involving the inflow portion of the ventricular septum are entirely related to the muscular portion of the septum and in older classifications have been called "muscular ventricular septal defects." Defects in this region may occur in any portion of the septum but mainly in one of two regions. The commonest site is that part of the ventricular septum which lies posterior to the papillary muscle of the conus and posterior to the membranous portion of the ventricular septum (Figure VI-33). From the right ventricular aspect, the defect lies beneath the posterior portion of the septal leaflet of the tricuspid valve. From the left ventricular aspect, the defect lies at the junction of the inflow and outflow por-

tions of the left ventricle and anterior to the posteromedial commissure of the mitral valve. Defects in this region tend to be single. This type of defect was seen by Crawford (1936) in a 40-year-old man who also had a gumma of the myocardium. The other common site is the apical region of the ventricular septum. Defects in this location may be single but have a tendency to be multiple and may involve much of the muscular septum (Figure VI-34).

When inflow defects are single, they are usually restricted to the apical region as in the cases reported by Weiss (1927), Mason and Hunter (1937), Konar and Sen Gupta (1954), and Heath and associates (1956), and in the case of a yak calf reported by Wimsatt and Lewis (1948). When multiple, they are usually distributed along the ventricular septum just behind the anterior wall of the heart. The uppermost of the defects may be in the outflow tract while the lowermost is at the apex of the heart. Commonly,

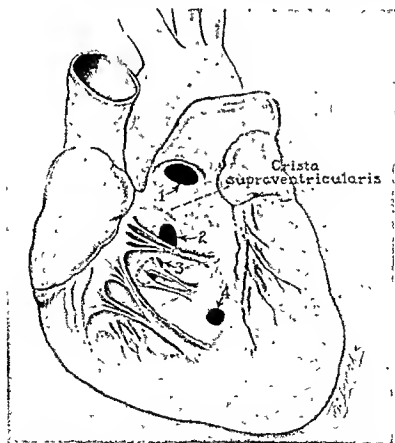


Figure VI-30 Common locations of defects in outflow portion of ventricular septum (1 and 2) and in inflow portion of ventricular septum (3 and 4). (From Kirkhn and associates, 1957. Reproduced by permission of C. V. Mosby Company.)

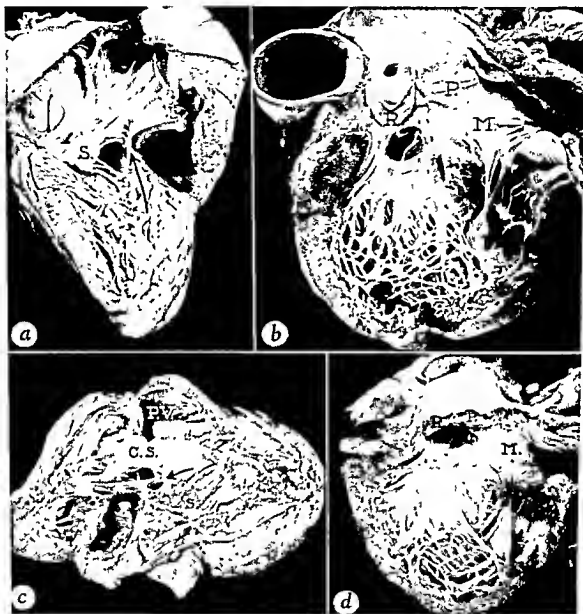


Figure VI-31. Two cases of ventricular septal defect related to ventricular outflow tracts which lie postero-inferior to crista supraventricularis.

a and *b*. Right and left sides, respectively, of heart with ventricular septal defect lying posterior to papillary muscle of conus (point of arrow in *a*. *S* indicates septal leaflet of tricuspid valve; *R*, right aortic cusp, *P*, posterior aortic cusp; and *M*, anterior mitral leaflet. (From Becu and associates, 1956. Reproduced with permission of Grune & Stratton, Inc.)

c and *d*. Defect involving outflow tract of ventricular septum and lying immediately postero-inferior to crista supraventricularis. This defect extends posteriorly to involve membranous portion of septum. Crossing the defect are chordae which insert into the papillary muscle of the conus (point of arrow in *c*. *C.S.* indicates crista supraventricularis; *S*, septal leaflet of tricuspid valve, and *P.V.*, pulmonary valve. In *d*, the defect is immediately beneath the right (*R*.) and posterior (*P*.) aortic cusps and immediately in front of the anterior mitral leaflet (*M*.). The chordae, which insert into the papillary muscle of the conus and are clearly seen in *c*, are also visible through the defect in *d*.

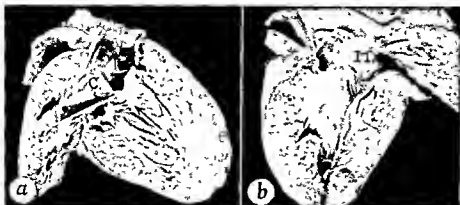


Figure VI-32. Ventricular septal defect related to outflow portion of ventricular septum and lying anterosuperior to crista supraventricularis. *a*. Right ventricle. The defect lies above the crista supraventricularis (C.) and immediately beneath the pulmonary valve. It is removed from the papillary muscle of the conus (point of arrow). *b*. Left ventricular aspect. The defect lies in the most anterior portion of the ventricular septum and is removed from the membranous portion which lies just in front of the anterior mitral leaflet (M.). The aortic valve is bicuspid. From a child who also had coarctation of the aorta. (From Kirklin and associates, 1957.

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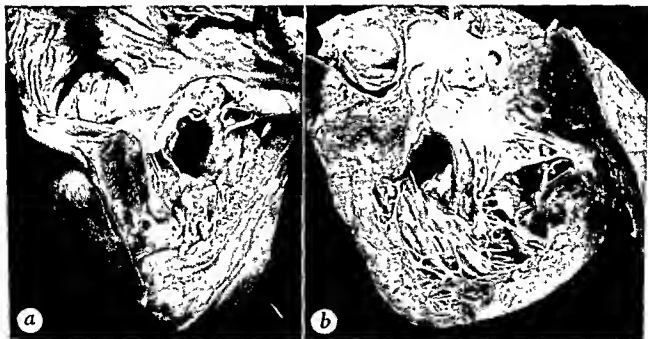


Figure VI-33. Ventricular septal defect involving inflow portion of ventricular septum and lying inferior to septal leaflet of tricuspid valve. (From Kirklin and associates, 1957. Reproduced by permission of C. V. Mosby Company.) *a*. Right side of heart. The defect is surrounded by muscle and lies inferior to the septal leaflet of the tricuspid valve. *b*. Left side of heart. Defect lies some distance from aortic valve and anterior to posteromedial commissure of mitral valve.

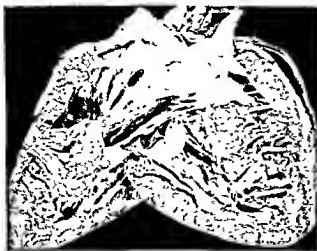


Figure VI-34. Multiple ventricular septal defects, involving muscular portion of ventricular septum. Probes lie in three of the multiple defects which extend from the apex to the outflow portion of septum.

hearts with such defects have great trabeculation not only of the right ventricle but also of the septal wall of the left ventricle. The course of the defect through the muscle may be tortuous, and careful inspection is sometimes necessary to make certain that a defect actually exists. Defects of the inflow part of the septum, whether single or multiple, may be associated with the common variety of defect in the outflow part of the septum (Mason and Hunter, 1937, Becu *et al.*, 1956, Kirklin *et al.*, 1957, Warden *et al.*, 1957).

DEFECTS COMMON TO OUTFLOW AND INFLOW PORTIONS OF VENTRICULAR SEPTUM

On rare occasions a large ventricular septal defect is seen which, when viewed from the right, lies under the septal leaflet of the tricuspid valve and extends upward to involve the membranous septum and beyond to the crista supraventricularis. From the left side, the defect lies beneath the posteromedial commissure of the mitral valve and the adjacent portion of the posterior leaflet of the mitral valve. The defect continues anteriorly to include the membranous portion of the septum. Such defects occupy the position of the inter-ventricular communication present in the complete variety of persistent common atrio-ventricular canal. They are to be distinguished from the latter malformation, however, by the intact atrioventricular valves and by absence of an atrial septal defect.

LEFT VENTRICULAR-RIGHT ATRIAL COMMUNICATIONS

Whereas the usual communication in ventricular septal defect related to the membranous septum is between the right and left ventricles, in some instances the left ventricle communicates, not with the right ventricle, but with the right atrium (Perry *et al.*, 1949). They may take either of two forms as follows (Figure VI-35): (1) The defect of the membranous septum may be continuous with a defect in the floor of the right atrium (Buhl, 1857, McCullough and Wilbur, 1944). (2) An opening in the septal leaflet of the tricuspid valve may be associated, and the edges of this opening may be fused to the right side of the margins of the ventricular septal defect. In this way, intraventricular communication is prevented but the left ventricle communicates instead with the right atrium (Perry *et al.*, 1949). In other instances (Gutzeit, 1922; Hemsath *et al.*, 1936), the ventricular septal defect is of the usual variety but the tricuspid valve is deformed. The septal deformity allows primary entrance of arterialized blood into the right ventricle but the valvular deformity allows regurgitation of some of the arterialized blood from the right ventricle into the right atrium.

RELATIONS OF CONDUCTION TISSUE TO DEFECTS

The conduction tissue of the heart appears to have a close relationship to those defects that lie in the outflow portion of the ventricular septum and posteroinferior to the crista supraventricularis. It has been observed at operation (Kirklin *et al.*, 1957) that trauma, either from a fixation-forceps or a needle, to tissue lying at the posteroinferior margin of such a defect, may cause ventricular asystole or prolonged heart block.

Although the relationship of the conduction system to ventricular septal defects has yet to be investigated in detail, nevertheless, observations on conduction disturbances during and subsequent to repair of ventricular septal defects support the view that the conduction system in hearts with such a defect is placed essentially as

it is in normally formed hearts, as described by Widran and Lev (1951). Thus, the *bundle of His* and its right and left branches may be related closely to defects that appear in the outflow tract of the right ventricle inferior to the crista supraventricularis. In such defects, the main bundle is located in the tissue forming the postero-inferior extremity of the defect while the beginning of the right branch of the bundle of His lies more or less parallel to the inferior edge of the ventricular septal defect, as the right branch runs forward toward the base of the papillary muscle of the conus. Beyond this, it turns downward along the ventricular septum at some distance from the position of the usual type of ventricular septal defect. The base of the papillary muscle of the conus, while grossly related to the position of the right branch, lies beyond the origin of fibers of the left branch. The fibers of the left bundle in the normal heart are so placed as to cross toward the left in the tissue inferior to the position of the type of defects under discussion. The *atrioventricular node*, lying above the base of the septal leaflet of the tricuspid valve and in the lowermost part of the atrial septum at a position anterior to the orifice of the coronary sinus, is not as intimately related to the position of ventricular septal defects as are the main bundle of His and its right and left branches. Defects in the outflow tract of the left ventricle that are superior to the crista supraventricularis and immediately inferior to the pulmonary valve are not closely related to the position of the bundle of His and its branches. Defects in the apex of the septum are not intimately related to the position of the conduction system. Those defects lying beneath the septal leaflet of the tricuspid valve may be related to the position of elements of the right branch of the bundle of His.

Incidence of All Types

In various reviews ventricular septal defects constituted about 10 per cent of all cardiac malformations. In 1949 Selzer reported 12 cases of ventricular septal defect which had been encountered among 7243 necropsies of persons of all ages. In addition, he reviewed certain collections of cases in the literature among which he found 80 cases of ventricular septal defect, exclusive of those designated as examples of the Eisenmenger complex; the material was from patients of all ages, except for the cases reported by Gibson and Clifton (1938) whose material had been obtained from infants and children. In

these collected series, Selzer encountered 80 cases of ventricular septal defect, 72 examples of atrial septal defect, and 40 examples of ventricular septal defect with pulmonary stenosis (tetralogy of Fallot). Ventricular septal defect was found among congenital malformations of the heart and great vessels of persons of all ages, in the following frequency: 4 of 44 (Nicholson, 1936); 11 of 73 (Philpott, 1936); 3 of 36 (Rannels and Propst, 1937); 6 of 49 (Roberts, 1937); 29 of 169 (Jacobius and Moore, 1938); 41 of 141 (Clawson, 1944, 15,597 necropsies); 20 of 223 (White, 1955, 15,000 autopsies); 32 of 357 (Fontana,

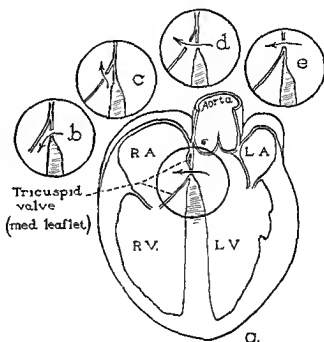


Figure VI-35. Diagrammatic representation of communication between left ventricle and right atrium, and associated conditions. *a.* Representation of defect in case reported by Perry and associates (1949). Note, in addition to defect in membranous part of ventricular septum, the double orifice of tricuspid valve. The adjacent edges of the two defects are fused so that the left ventricle communicates with the right atrium. *b.* Usual type of defect involving membranous part of ventricular septum, with communication between two ventricles. *c.* Double orifice of tricuspid valve involving septal or medial leaflet. *d.* Defects in cases reported by Gutzelt (1922) and by Hemsath and associates (1936). As in *a*, defect in membranous part of the ventricular septum is associated with double orifice of tricuspid valve. In contrast to conditions in *a*, edges of two defects are not fused. *e.* Defects in cases reported by Buhl (1857) and by McCullough and Wilbur (1944). In contrast to conditions in *a* and *d*, defect of membranous part of ventricular septum lies above orifice of tricuspid valve and is associated with a defect in floor of right atrium. The tricuspid valve is normal. (From Perry, E. L., Burchell, H. B. and Edwards, J. E., *Proc. Staff Meet., Mayo Clin.*, 24:198-206, 1949.)

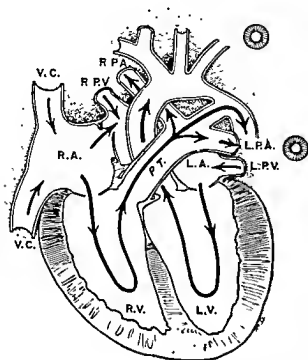


Figure VI-36. Central circulation during normal fetal life. It is important to recognize that the resistance to systemic flow is essentially the same as the resistance to pulmonary flow. The pressures in the two ventricles and in the pulmonary trunk and aorta are essentially equal. Blood flows from ductus arteriosus into descending aorta. The circles to the right of the diagram indicate the relative resistance to systemic flow (upper circle) and to pulmonary flow (lower circle).

1957). Among 336 necropsies on infants up to 1 year of age, exclusive of stillbirths, Terplan and Sanes (1936) found 21 instances (6.3 per cent) of congenital malformations of the heart, including 4 examples of ventricular septal defect.

Relative Incidence of Various Types

Of 50 specimens with ventricular septal defect reported from the pathologic collection of the Mayo Clinic by Becu and associates (1956), in 40 the defect involved the outflow portion of the ventricular septum. In 35 the defect lay postero-inferior to the crista supraventricularis while in 4 the defect was anterosuperior to the crista. In 10 cases single defects were present in the inflow portion of the ventricular septum; in 4 of these the defect was related to the atrioventricular valves while in 6 it was in the apical portion of the septum. One patient had two defects, one in the outflow portion of the ventricular septum posterior to the crista supraventricularis and the other in the inflow portion in relation to the atrioventricular valves. In 27 of a series of 36 surgical

cases of ventricular septal defect, which are not included in this collection reported by Becu and associates, Kirklin and associates (1957) found that the defect was restricted to the outflow tract. In 25 the defect was postero-inferior to the crista supraventricularis and in 2, anterosuperior to it. In the other 11 cases the defect was related to the ventricular inflow tracts, and in 8 of these it was further related to the atrioventricular valves. In 1 of the 3 other cases, the defect was in the apical portion of the inflow part of the ventricular septum; and in 2, multiple defects involved the apical region as well as the muscular part of the outflow portion of the ventricular septum. Warden and associates (1957) analyzed hearts with ventricular septal defect which they had observed at operation. If the types of defects listed are classified according to our terminology, 84 hearts had ventricular septal defect without pulmonary stenosis. In 71 of these, the defect was in the outflow portion of the ventricular septum postero-inferior to the crista supraventricularis, in 5 the defect lay superior to the crista supraventricularis; in 5, in the inflow tract in relation to the atrioventricular valves; and in 3, in the apical portion of the ventricular septum. Two of the last 3 hearts had multiple defects.

Sex Distribution

Among patients with ventricular septal defect males predominate slightly. Among Fontana's patients in the Mayo Clinic series 18 were male and 11 were female. Fontana reviewed the reports of Selzer (1949) and of Selzer and Laqueur (1951). Of the 118 patients in whom the sex was given, 62 were male and 56 were female.

Functional and Structural Effects in Uncomplicated Cases

CIRCULATION IN FETUS

During normal fetal life systolic pressures in the two ventricles are essentially equal as are the pressures in the systemic and pulmonary arteries (Hamilton *et al.*, 1937; Ardran *et al.*, 1952; Reynolds, 1956; Figure VI-36). Minor differences of magnitudes in pressure may accompany blood flow through the ductus arteriosus from the pulmonary arteries into the descending aorta. In fetuses with ventricular septal defect of various sizes, the circulation probably does not differ from that

in the normal fetus, since the ductus arteriosus is available for normal flow.

POSTNATAL CIRCULATION

The following discussion of the functional features of the postnatal circulation of patients with ventricular septal defects of various sizes and at different stages in the disease is derived in part from reports (Bing *et al.*, 1947; Adams, 1952; Swan and Wood, 1953; Soulié *et al.*, 1953; Swan *et al.*, 1954; Brown *et al.*, 1955; Dammann and Ferencz, 1956) and in part from data obtained in the Physiology Laboratory of the Mayo Clinic (made available by Drs. Earl H. Wood, H. J. C. Swan, H. F. Helmholz, Jr., and others).

After birth, when the tendency for pulmonary vascular resistance to fall is manifest (Reynolds, 1956), the size of the defect becomes of paramount importance. A small defect presents a high degree of resistance to blood flow (Figure VI-27*a*). It constitutes an obstruction between the left ventricle on one hand, and the right ventricle and the pulmonary arteries on the other. The left ventricle is then obviously not in free communication with the lesser circulation, and a differential in pressure is possible in the two compartments (Baldwin *et al.*, 1946; Dexter *et al.*, 1947; Vandam *et al.*, 1947; Handelsman *et al.*, 1948; Cournand *et al.*, 1949). This happens as the pulmonary vascular resistance falls toward normal postnatal levels, and normal postnatal changes of the pulmonary arteries and arterioles become manifest. The small defect prevents large volumes of blood from shunting from the left ventricle to the lesser circulation. The pulmonary and right ventricular pressures are normal. A large defect, having about the same diameter as the aorta (Selzer, 1949), allows free communication between the left ventricle on one hand and the right ventricle and pulmonary arteries on the other. It lacks the obstructive character of the small defect (Figure VI-27*b* and *c*).

The blood flows predominantly into the system having the lower resistance. The tendency for the pulmonary vascular resistance to fall in the normal infant after birth is paralleled to some extent by the condition in patients with ventric-

ular septal defect (Dammann and Muller, 1953; Dammann and Ferencz, 1956). Consequently, the classic shunt in infants with large ventricular septal defect is entirely in a left-to-right direction. Because the pulmonary flow is so much greater than the systemic flow and because the two ventricles are essentially the same compartment, the pulmonary pressure tends to become elevated and to approach the systemic systolic pressure. In infants, the pulmonary diastolic pressure is usually significantly lower than the systemic diastolic pressure. With time, the magnitude of the left-to-right shunt tends to decrease as a consequence of progressive elevation in pulmonary arterial resistance. As the pulmonary arterial resistance rises to the general range of systemic arterial resistance, a right-to-left shunt

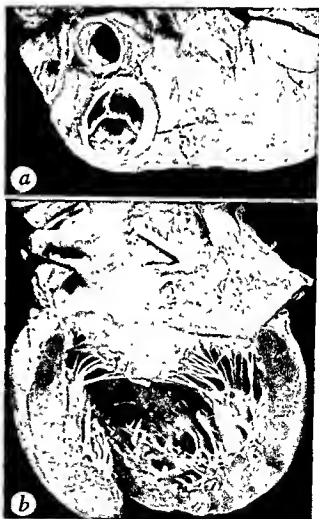


Figure VI-37. Large ventricular septal defect in a male infant 2 years of age. *a* Pulmonary trunk and aorta from above. The pulmonary trunk is obviously wider than the caliber of the normal aorta. *b* Left atrium and left ventricle. Note secondary endocardial sclerosis of left atrium and left ventricle, and moderate dilatation of both chambers.



Figure VI-38 Aneurysm of fossa ovalis in 5-year-old boy with ventricular septal defect and large left-to-right shunt at ventricular level. *a*. Right atrial aspect. The aneurysm of the fossa ovalis bulges into the right atrium. *b*. Left atrium. Above the mitral valve lies the cavity of the aneurysm of the fossa ovalis which protrudes into the right atrium

may become manifest. The right-to-left shunt may eventually become dominant. It must be emphasized that pulmonary vascular resistance, in the range of systemic vascular resistance, results from complicating organic changes that takes place in relatively large muscular arteries of the lungs. These changes will be described in another section and may be regarded as complications rather than as an integral part of the pulmonary vascular response in ventricular septal defect.

In uncomplicated cases of ventricular septal defects, left atrial and pulmonary capillary (pulmonary "arterial wedge") pressures are normal (Calazel *et al.*, 1951). When elevation does occur, however, it is probably a consequence either of left ventricular failure or of associated mitral insufficiency. In either event, such a change is best thought of as a complication rather than as a usual manifestation of the dynamics of the circulation in the malformation.

STRUCTURAL CHANGES IN HEART AND PULMONARY VESSELS

Small Defects. In hearts with small defects of the ventricular septum the thickness of the two ventricles is usually normal, but the left ventricle may be slightly enlarged. The pul-

monary trunk is not dilated. The right ventricle opposite the ventricular septal defect and also the septal leaflet of the tricuspid valve may show hyaline focal thickenings (Weinstein, 1926). These are tissue responses to the trauma of the jet of blood flowing through the small opening from a ventricle having a high pressure to one having a low pressure ("jet lesions"). The small pulmonary vessels are essentially normal in structure (Edwards, 1957).

Large Defects. In hearts with large ventricular septal defects, the most striking change is hypertrophy of the right ventricle. The right ventricular hypertrophy is the anatomic reflection of the increased pulmonary and right ventricular systolic pressures which are equal to or approach those of the greater circulation. The pulmonary arterial system shows abnormalities at all levels in patients with large ventricular septal defects, as well as in those with wide, patent ductus arteriosus in which the abnormal channel allows free communication between the aorta and pulmonary arteries. In each of these malformations

the pulmonary trunk is considerably wider than normal and considerably wider than the ascending aorta (Figure VI-37a). The latter is about normal in caliber, as represented by the cases of Rosedale (1935) and of Warner (1944). Young patients have no other significant changes in the elastic pulmonary arteries while older patients may have atheroma of the elastic arteries of the lungs.

The left ventricular wall is somewhat thicker than normal, but the most striking change is enlargement of the chamber. This change is especially prominent in patients in whom a large left-to-right shunt existed during life. The left atrial chamber also may be enlarged. The endocardium of the chambers on the left side, particularly that of the left atrium, may show fibrous thickening or "secondary endocardial sclerosis" (Figure VI-37b), apparently as a result of stretching of the endocardium of the enlarged chamber. The foramen ovale may be closed or may show valvular-competent patency. The author has examined 2 hearts which had a foramen ovale, and an aneurysm of the fossa ovalis which protruded into the right atrium. This finding serves as anatomic support for the existence, in some cases of ventricular septal

defect (Figure VI-38), of higher pressure in the left than in the right atrium.

Two types of change occur in the smaller vessels, that is, in the muscular arteries and the arterioles. The first type I have termed (Edwards, 1957) a *high-resistance, high-reserve* system; the other, a *high-resistance, low-reserve* system (Figure VI-39). The former type is the usual change in patients less than 2 years of age, but may be seen in patients of any age. With time, however, the pulmonary vascular bed tends to change from the *high-resistance, high-reserve* type of system to the *high-resistance, low-reserve* type.

The *high-resistance, high-reserve* type of vascular bed is essentially like that of the normal fetus (Civin and Edwards, 1951; Dammann and Ferencz, 1956). It has the following characteristics: The muscular arteries of all sizes have thick muscular medial layers associated with thick elastic laminae (Figure VI-40a and b). At times the thickness of the adventitia is increased by dense collagen. The arterioles show thick muscular medial layers and often well-defined elastic layers, as well as suggestions of thickened adventitia. The thickening of the muscular medial layer extends for varying distances along the arterioles, but consistently the first portion of the arterioles is most strikingly involved by the medial thickening and luminal narrowing. At times the muscle fibers of the thickened arterioles are vacuo-

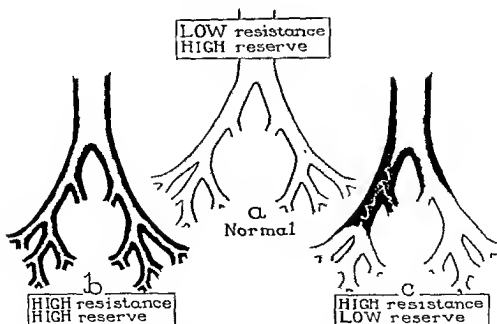


Figure VI-39. Normal pulmonary arterial system and the two basic types in which a free communication exists between the ventricles or great arteries (From: Edwards, 1957. Reproduced with permission of Grune & Stratton, Inc.)

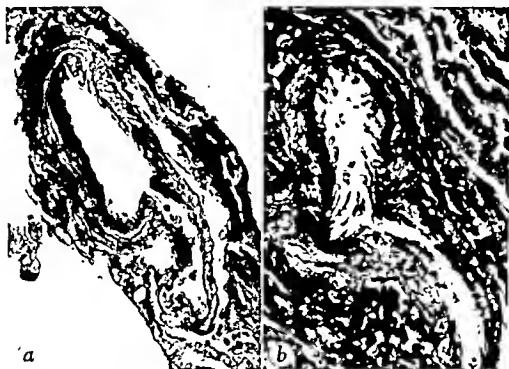


Figure VI-40. Pulmonary small muscular arteries and arterioles from patients with large ventricular septal defects (From Edwards, 1957. Reproduced by permission of Grune & Stratton, Inc.) *a* Small muscular artery and arteriolar branch from 8-month-old infant with large ventricular septal defect and pulmonary hypertension. Medial hypertrophy (Verhoeff's elastic tissue stain, counterstained with van Gieson connective tissue stain, X 330) *b* Small muscular artery and arteriolar branch from 6-year-old child with multiple large ventricular septal defects. Medial hypertrophy. Suggestion of intimal fibrous thickening at origin of arteriole. (ElvG; X 330.) In *a* and *b* the pulmonary bed was designated as that of a high-resistance, high-reserve type (see Figure VI-39).

lated. Intimal fibrous lesions are usually absent or, if present, are few and are restricted to small arteries or arterioles.

In the high-resistance, low-reserve pattern, the large muscular arteries show characteristic obliterative intimal lesions. The small muscular arteries and arterioles may show similar lesions, but the majority have thin walls and dilated lumina. The intimal lesions involve arteries as large as 300 micra in diameter. These lesions frequently show a plexiform arrangement in individual cross-sections. In serial sections, the involved segment of artery shows irregularly deposited collections of young connective tissue, resulting in a markedly narrowed lumen with irregular configuration. Older lesions are acellular and hyalinized. The irregular spaces in the lumen of the artery with intimal thickening may suggest the appearance of an organized thrombus. In my opinion, the characteristic lesion is not an organized thrombus, although organized thrombi may exist in the same case.

The intimal arterial lesions which may be seen in ventricular septal defect are observed also in some cases of patent ductus arteriosus, atrial septal defect and so-called primary pulmonary hypertension (zur Linden, 1924). Some authors have claimed that these lesions are glomus-like congenital malformations. Others have suggested that they are arteriovenous communications (Spencer, 1950; Brewer, 1955). This latter suggestion implies that cyanosis which may appear in ventricular septal defect is a consequence of a shunt through these hypothetical channels. Neither of the claims can be supported, since the lesions may readily be demonstrated by serial sections to be confined to arteries (zur Linden, 1924; Evans, 1951; Edwards, 1955; Whitaker *et al.*, 1955; Heath *et al.*, 1956).

A remarkable difference is evident in the small arteries and arterioles between lungs of the high-resistance, low-reserve type and those of high-resistance, high-reserve pattern. Whereas in the latter the arteries and arterioles show medial hy-

hypertrophy with correspondingly narrow lumina, most of the small vessels of the high-resistance, low-reserve type of lung show wide lumina and thin walls. The thinning and dilatation of the vascular walls are universal, occurring both beyond obstructed arteries and in areas where arteries are not obstructed. In some cases, the dilatation of the small arteries and of the arterioles may reach extreme proportions with sacular formation. When these dilated vessels lie near the air spaces, they may herniate into them. Rupture may cause hemoptysis in patients with this type of pulmonary vascular bed (Heath *et al.*, 1956). Brewer (1955) has indicated that some of these dilated vessels represent collateral channels arising from pulmonary arteries above the sites of obstructed lumina to the vascular bed beyond. Heath (1937) has suggested that some are collateral channels from the bronchial arterial system. The majority of the dilated vessels are normal at the sites of origin and termination.

The location of the intimal occlusive lesions in relatively large arteries correlates well with observations in postmortem angiographic studies, when the arteries show a blunted configuration (Hultgren *et al.*, 1953; Yu *et al.*, 1954). This has been called a "pruning" effect by Evans (1951). In addition to the intimal lesions, necrosis and thrombosis may be observed in the large muscular arteries (Old and Russell, 1950; Edwards and Chamberlin, 1951; Kipkie and Johnson, 1951; Symmers, 1952; Cosh, 1953; Hicks, 1953).

The pulmonary vascular bed with occlusive intimal arterial lesions often displays a high resistance to flow. The reason is that the occluded arteries are large, often being 0.3 mm. or wider in diameter in adults; and, therefore, they channel blood to a relatively large part of the pulmonary tissue. With multiple lesions of this type, a considerable amount of the pulmonary vascular bed is eliminated from the effective perfusion channel of the lesser circulation, even allowing for some collateral circulation to this area from the bronchial arteries. As far as the functional capacity of the pulmonary vascular bed is concerned, it is as though portions of the lung had been extirpated. Ferguson and Varco (1955) have removed portions of the lung and produced pulmonary hypertension by reducing the total capacity of the vascular bed and additionally by increasing the flow to the remaining pulmonary tissue.

Clinical Features

The varied clinical pictures among patients

with ventricular septal defect have been reviewed by Joly and associates (1951) and by Dammann (1955). Patients with small ventricular septal defects, as already indicated, have normal pulmonary and atrial pressures and relatively small shunts. In addition, the walls of the two ventricles are essentially normal in thickness. The resulting clinical picture is one of good tolerance to normal conditions and exercise, as shown by the roentgenogram and electrocardiogram. The major abnormalities revealed in the clinical examination are related to the shunt through a small opening and between high and low pressure systems. These are reflected in a systolic murmur and thrill which are usually most intense at the left of the sternum at the level of the third or fourth intercostal space. This type of lesion has been said to be representative of ventricular septal defect and is sometimes spoken of as the "maladie de Roger."

This type of case is now recognized as being far less common than large ventricular septal defects. Whereas patients with small ventricular septal defects are usually asymptomatic, having abnormalities detected only on physical examination, patients with large defects usually have symptoms. In earlier stages the symptoms result from pulmonary hypertension and from left ventricular failure caused by the left-to-right shunt. These manifestations are followed by symptoms resulting from the pulmonary hypertension and complicating right-to-left shunt. Cyanosis is not present during infancy and childhood. Some patients may seem normal during this period, while others manifest a variety of pulmonary symptoms, often called "attacks of bronchitis or pneumonia" or both. These lesions, in all probability, represent attacks of pulmonary edema.

Patients who survive infancy and childhood usually achieve a relatively stabilized state during which they have a left-to-right shunt of varying magnitude. In this stage they may be asymptomatic or, more often, dyspneic on exertion, and the thoracic roentgenogram clearly shows prominence of the pulmonary arterial shadow. The electrocardiogram indicates biventricular hypertrophy with predominant enlargement of the left ventricle and left atrium. In some cases right bundle-branch block may be present (Marsico *et al.*, 1955).

If occlusive intimal lesions appear in the pul-

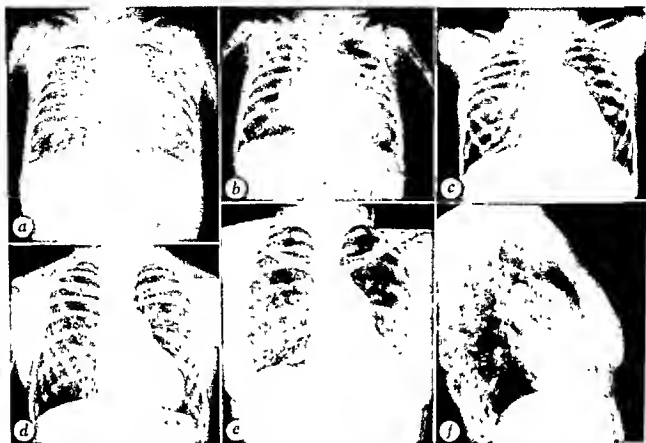


Figure VI-41. Thoracic roentgenograms of patients of different ages with large ventricular septal defects showing changes in the picture with progressive age as the large left-to-right shunt of early life eventually gives way to a right-to-left shunt. *a*, From a 4½-month-old infant. *b*, From a 7-month-old infant. *c*, From a 2-year-old child. *d*, From a 6-year-old child. *e* and *f*, From a 33-year-old woman.

monary vessels, the complicating right-to-left shunt may be responsible for cyanosis (Donzelot *et al.*, 1949). The thoracic roentgenogram, which in early stages shows evidence of cardiac enlargement and pulmonary engorgement, at this late stage may show only a prominent shadow of the pulmonary trunk (Figure VI-41). The pulmonary fields become more radiolucent as evidence of reduction in magnitude of the left-to-right shunt (Dammann and Muller, 1953; Maham, 1949; Wittenborg and Neuhauser, 1955; Dammann and Ferencz, 1956). The electrocardiogram shows evidence of predominant right ventricular hypertrophy, a pulmonary diastolic murmur of pulmonary valvular insufficiency may be heard, and a precordial systolic murmur is usually heard and a thrill palpable. Hemoptysis may complicate this stage of the disease and is perhaps derived from enlarged bronchial arteries (Heath, 1957). Patients who have a right-to-left shunt of sufficient magnitude to cause cyanosis may show polycythemia, digital clubbing, and the fainting attacks of cerebral anoxia which are common in other

forms of congenital cardiac disease having chronic desaturation of the systemic arterial blood.

Associated Conditions

Ventricular septal defect is often associated with other malformations, including persistent truncus arteriosus, complete transposition of the great vessels, corrected transposition of the great vessels, and the so-called tetralogy of Fallot (ventricular septal defect with pulmonary stenosis). Excluding such combinations of malformations, Becu and associates (1956) studied at necropsy a group of 50 hearts with ventricular septal defect in which no operation had been performed. In 36, significant cardiovascular malformations were not associated with the ventricular septal defect. In the other 14, the malformations associated with the ventricular septal defect did not form recognized anatomic complexes of cardiac malformations. The four major associated malformations observed were atrial septal defects of the usual variety, patent ductus arteriosus, coarctation of the aorta, and vascular rings. In . . . instance,

the vascular ring when present was characterized by a right aortic arch with a retro-esophageal segment and a left-sided descending aorta (Figure VI-42).

Among 36 hearts with ventricular septal defect which were observed at operation, Kirklin and associates (1957) found 4 with coexistent atrial septal defect, 3 with persistent left superior vena cava and 1 each with patent ductus arteriosus, congenital mitral stenosis and right aortic arch. Bowers and associates (1955) described the clinical findings and those at cardiac catheterization in a child with ventricular septal defect and patent ductus arteriosus. Bond (1951) reported 2 cases of ventricular septal defect which had been reported in the literature as examples of the Eisenmenger complex. One patient had patent ductus arteriosus associated with the ventricular septal defect, the other, mild coarctation of the aorta. Warden and associates (1957) reported on

87 cases of ventricular septal defect observed at operation. In 3 the ventricular septal defects were multiple and in 3 atrial septal defects coexisted. In 4 hearts the defect was associated with patent ductus arteriosus; in 2, coarctation of the aorta; in 1, corrected transposition of the great vessels, in 5, persistent left superior vena cava; and in 7, endocardial fibroelastosis. It is probable that the last condition may not have represented a malformation but rather secondary endocardial sclerosis, since this is relatively frequent in patients who have ventricular septal defect with large left-to-right shunts and concomitant dilatation of the left ventricle.

Kurtz and associates (1927) observed ventricular septal defect and moderate coarctation of the aorta in a 14-year-old boy. Espino-Vela and Mata (1956) described a case of ventricular septal defect with a right aortic arch and retro-esophageal segment. They also described 2 other



Figure VI-42. Right aortic arch of usual pattern, associated with ventricular septal defect. *a* Right ventricle and beginning of pulmonary trunk have been opened; a probe has been placed in the ventricular septal defect which lies just beneath the crista supraventricularis. The probe has passed into the aorta and has appeared through the right common carotid artery. The aortic arch is over the right bronchus. The branches which arise from the aorta are the left common carotid artery, the right common carotid artery (containing probe) and, beyond it, the right subclavian artery, in that order. The left subclavian artery lies to the left of the trachea and has arisen from the back of the aorta as its fourth branch. This is illustrated in *b*. *b*. Posterior view of mediastinal structures. Aorta has passed over right bronchus and has reached left side of body by passing behind esophagus. It descends to the left of the esophagus. The left subclavian artery arises from the junction of the descending aorta and the right aortic arch.

eases with a peculiar narrowing of the ascending aorta. The author has observed an example of so-called double orifice of the mitral valve in association with ventricular septal defect, in which it seemed that the extra opening may have been responsible for significant mitral insufficiency.

Differential Diagnosis

A small ventricular septal defect in a patient who is essentially asymptomatic and has only a murmur and thrill, is to be distinguished from pulmonary valvular stenosis and intact ventricular septum.

In infants suffering from excessive pulmonary flow and attacks of pulmonary edema, many conditions must be considered. These include conditions that cause left ventricular failure in infancy, such as patent ductus arteriosus, single ventricle without pulmonary stenosis, certain forms of persistent truncus arteriosus, tricuspid atresia without obstruction to pulmonary flow, origin of both great arteries from the right ventricle, and the complex of ventricular septal defect, subaortic stenosis and aortic obstruction. Also included are completely persistent common atrioventricular canal, coarctation of aorta, stenosis at or near the aortic valve, anomalous origin of left coronary artery from the pulmonary trunk, and myocarditis. In addition one must consider conditions that cause pulmonary venous obstruction, such as congenital mitral stenosis, cor triatriatum, and primary endocardial sclerosis (Ash *et al.*, 1939, Ferenz *et al.*, 1954; Edwards, 1954), and also ventricular septal defect and mild pulmonary stenosis in patients having only, or predominantly, a left to-right shunt.

The clinical picture in infants or children with ventricular septal defect and large left-to-right shunts but no striking evidence of pulmonary edema may be confused with that of patients who have patent ductus arteriosus, atrial septal defect, single ventricle without pulmonary stenosis, or so-called primary pulmonary hypertension of infancy and childhood (Berthrong and Cochran, 1955).

In patients with ventricular septal defect without pulmonary stenosis, who have obvious cyanosis, an entirely different group of conditions must be considered. Paramount among these are ventricular septal defect with pulmonary stenosis (tetralogy of Fallot), atrial septal defect with pulmonary hypertension and right-to-left shunt, patent ductus arteriosus with "reversal of flow" (Figure VI-43), single ventricle with pulmonary

stenosis, single ventricle without pulmonary stenosis but with occlusive changes in the pulmonary vascular tree, and total anomalous pulmonary venous connection. So-called primary pulmonary hypertension with a right-to-left shunt at a patent foramen ovale should also be considered.

It must be borne in mind that certain conditions may be associated with ventricular septal defect, and that sometimes only the associated condition or only the defect is recognized. For example, in the patient with ventricular septal defect and coexistent atrial septal defect the findings at cardiac catheterization usually will indicate the presence of the atrial septal defect, but may not indicate evidence of a left-to-right shunt at ventricular level. Similarly, in a patient with a ventricular septal defect and patent ductus arteriosus, cardiac catheterization may indicate the presence of the ventricular septal defect but not the patent ductus arteriosus.

Prognosis

While the older literature leads one to regard ventricular septal defect as a condition which ordinarily causes little difficulty in early life, more recent studies (Ash *et al.*, 1939, Marquis, 1950, Edwards, 1950b; Engle, 1954; Ferenz *et al.*, 1954; Harned *et al.*, 1955; Becu *et al.*, 1956) indicate that this condition may be lethal in early infancy. The prognosis in ventricular septal defect seems basically to depend on the size of the defect, patients with small defects generally living longer than patients with large defects (Selzer, 1949). Selzer found that among 38 patients with small or medium-sized ventricular septal defects only 5 died when less than 1 year of age, 13 died between the ages of 1 and 15 years, and 20 after the age of 15. Among 31 patients with large or extremely large ventricular septal defects, 13 had died when less than 1 year of age, 8 died between the ages of 1 and 5 years, and 10 after the age of 15 years.

Becu and associates (1956) studied 34 hearts in which a single ventricular septal defect was the only significant cardiovascular malformation. These hearts were in the pathologic collection of the Mayo Clinic prior to the era of surgery for ventricular septal defect. They found that in 19 patients, death was related to the ventricular septal defect. In the remaining 15, death was attributed to some other condition, usually a major malformation in another organ. Of the 19 patients who died as a result of the defect, 12 were less than 1 year old; 4 were 14, 18, 33 and 55 years of age, respectively.

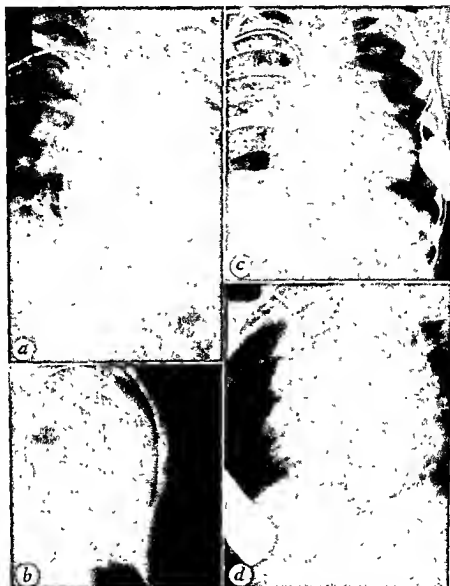


Figure VI-43. Differences of position in catheter which has entered aorta during right ventricular cardiac catheterization in a patient with ventricular septal defect and in a patient with patent ductus arteriosus. These differences may be used as important differential points between the two conditions.

a and *b*. Ventricular septal defect. Anteroposterior and lateral views respectively. In the anteroposterior roentgenogram the catheter has passed through a ventricular septal defect from the right ventricle into the aorta. A distinguishing feature of this pattern is that the downward limb of the catheter lies farther to the patient's left than does the upward limb of the catheter. In the lateral roentgenogram the catheter in the aorta takes a sweep to a substernal position before arching backward.

c and *d*. From a patient with patent ductus arteriosus. In the anteroposterior roentgenogram the downward limb of the catheter in the aorta lies to the patient's right of the upward limb of the catheter. In the lateral roentgenogram the catheter does not approach the sternum as it enters the aorta. The author is indebted to Dr. E. H. Wood for the illustrations.

Complications

Bacterial Endocarditis. Among patients with small ventricular septal defects, the most significant complication is bacterial endocarditis; this complication also may affect large ventricular septal defects (Sprenkel and Stewart, 1935; Millman and Kornblum, 1936). Bacterial endocarditis tends to develop along points of trauma (Furlong, 1944). The infection may start on margins of the septal defect, on the tricuspid valve, or on the ventral wall of the right ventricle, and extend to other points. From the left ventricular side, it may extend to the aortic valve.

Of 555 cases of congenital cardiac disease of clinical significance analyzed by Abbott (1925), 40 were examples of ventricular septal defect and 16 of these (40 per cent) were complicated by bacterial endocarditis. Gelfman and Levine (1942) studied 453 cases of congenital cardiac disease, 35 were complicated by bacterial endocarditis. Of 164 patients of all ages with ventricular septal defect, 10.4 per cent (17 patients) had bacterial endocarditis; of the remaining patients with all other types of congenital cardiac disease, only 6.2 per cent had this complication. Of the 453 patients, 181 were 2 years of age or older at the time of death; 31 of the 181 had ventricular septal defects and 13 of the 31 (42 per cent) also had bacterial endocarditis. This incidence of bacterial endocarditis complicating ventricular septal defect, therefore, corresponds to that reported by Abbott. In only 5 of the cases of Gelfman and Levine in which the patients were 2 years of age or older did the bacterial infection involve the margins of the defect.

The higher incidence of bacterial endocarditis complicating ventricular septal defect in the older group bears out, in a broad way, the maxim that the longer the patient with congenital cardiac disease survives, the greater his chance of acquiring bacterial endocarditis. This is related to the chance of repeated exposure to bacteremia with increasing age.

Furlong (1944) and others have expressed the opinion that a complicating infection is more likely to develop in hearts in which the shunted blood has a traumatizing effect than in hearts in which there is no such influence. Blumgart (1933) pointed out that since the shunt in ven-

tricular septal defect is from the left to the right ventricle, emboli from bacterial endocarditis usually involve the pulmonary circulation rather than the systemic circulation, and that positive cultures of the peripheral blood may be absent. Characteristically bacterial endocarditis involving the right side of the heart has the following features: (1) presence of a cardiac lesion in a right cardiac chamber; (2) evidence of generalized infection; (3) no evidence of peripheral emboli in the greater circulation but, instead, symptoms and signs of protracted pulmonary infection caused by multiple septic pulmonary infarcts. Only in far-advanced disease, when there is necrosis of the septic pulmonary infarcts, do organisms tend to reach the systemic circulation.

Espino-Vela and Mata (1956) observed closure of a ventricular septal defect by the adherent septal leaflet of the tricuspid valve. They reasoned that the adhesion was the result of healed bacterial endocarditis.

Pulmonary Edema. Pulmonary edema is the major cause of death among patients with large ventricular septal defects who die in infancy, probably as a result of left ventricular failure.

Occlusive Pulmonary Vascular Changes. In the review of the structural changes in the pulmonary vascular bed in patients with ventricular septal defect, it was pointed out that, among those having large ventricular septal defects, severe occlusive changes may ultimately result from thickening of the intima of the muscular arteries of the lungs. This development should be looked on as a complication. The occlusive changes are responsible for development of a right-to-left shunt, attendant cyanosis and anoxic attacks, and rarely (Banmgartner and Abbott, 1929), cerebral abscess in the absence of bacterial endocarditis.

Cardiac Failure. In addition to left ventricular failure giving rise to pulmonary edema, chronic congestive heart failure is a potential complication in patients with large ventricular septal defects. Usually this type of heart failure occurs in adult life (Dalrymple, 1848; Eisenmenger, 1897; Weiss, 1927; Stewart and Crawford, 1933).

Right-to-Left Shunt. It has already been noted that intimal lesions in the pulmonary muscular

arteries may raise the resistance to pulmonary flow to exceed ordinary systemic resistance. A chronic right-to-left shunt develops which may be associated with cyanosis, clubbing of the digits, and anoxic attacks indicated by fainting. If for some reason the systemic resistance should fall, the right-to-left shunt may be accentuated, especially in a patient having high pulmonary vascular resistance. This may account for intensification of cyanosis and for death in certain patients with ventricular septal defect during the terminal phases of pregnancy (Tucker and Kinney, 1945; Bond, 1951). Delivery constitutes a hazard to the patient with ventricular septal defect, since it may be accompanied by a fall in systemic blood pressure (Mendelson and Pardee, 1941; Jensen, 1949, Kerr and Sodeman, 1951). *Paradoxical embolism* may occur in the presence of a right-to-left shunt (Richards and Cohn, 1954). Such an embolism to the coronary system may explain the episode of acute myocardial infarction in the clinical case of Vesell (1954) of a 34-year-old man with ventricular septal defect.

Complete Heart Block. Complete heart block may be associated with ventricular septal defect, and occasionally may be suspected before birth of the infant if the fetal heart sounds have a slow rate (Massey, 1948). In some patients, even in those having this abnormality before birth, the conduction disturbance may represent a complication rather than an accompanying finding in this disease (Burchell, 1949; Rogers and Rudolph, 1951).

In a personal communication to the author, Dr. Weldon J. Walker has indicated that, in patients with ventricular septal defect and complete heart block, the incidence of corrected transposition of the great vessels is inordinately high. He also pointed out that, in the case of complete heart block reported by Yater and associates (1933), the illustrations indicate the coexistence of corrected transposition and ventricular septal defect. In that case, study of serial sections of the conduction system gave evidence that a connection between the atrioventricular node and the bundle of His was absent.

Hoarseness. Hoarseness may complicate the course of a patient with large ventricular septal defect, as in the case of Baumgartner and Abbott (1929). The hoarseness results from paralysis of the left vocal cord and sim-

ulates that seen in other cardiac conditions, either acquired or congenital, in which pulmonary hypertension forms a part of the disease.

Pulmonary Arterial Aneurysm. Pulmonary arterial aneurysm may complicate the pulmonary hypertension that accompanies large ventricular septal defect (Richards and Cohn, 1954). In Johannsen and Connor's case (1948) the defect was associated with a patent ductus arteriosus.

Aortic Insufficiency. In a number of instances aortic insufficiency has been associated with ventricular septal defect (Taussig and Semans, 1940; Hurst and Schemm, 1948; Soulié *et al.*, 1949; Ash and Murphy, 1950; Ascenzi *et al.*, 1951; Danaraj, 1956; Winchell and Bashour, 1956). In these cases the defect was located immediately beneath the aortic valve, and the murmur simulated that of classic patent ductus arteriosus. In some instances, operation was performed because a diagnosis of patent ductus arteriosus was made. The right cusp shows fibrous thickening and some retraction (Figure VI-44) which in part result from the trauma of turbulence of the blood at the aortic valve (Edwards and Burchell, 1957).

The association of aortic insufficiency and ventricular septal defect must be distinguished from the combination of aortic sinus aneurysm and ventricular septal defect (Morgan and Burchell, 1950; Burchell and Edwards, 1951).

Surgical Correction

Methods have been perfected for temporary extracorporeal circulation during which the interior of the heart may be exposed and ventricular septal defects closed (Kirkin *et al.*, 1955; Lillehei *et al.*, 1955; DuShane *et al.*, 1956; Kirkin *et al.*, 1957; Warden *et al.*, 1957). At present patients with small ventricular septal defects are not generally regarded as candidates for surgical closure of defects, because of the good prognosis without surgical correction. These patients, however, should have prophylactic treatment against bacterial endocarditis, just like patients with residual lesions of rheumatic fever. Surgical closure of the defect is indicated in patients with large ventricular septal defects, and particularly in children with large left-to-right shunts. In some children and in most adolescents and adults the indications are not as clear-cut, since severe occlusive changes may have developed in the pulmonary vessels. Such patients have varying de-

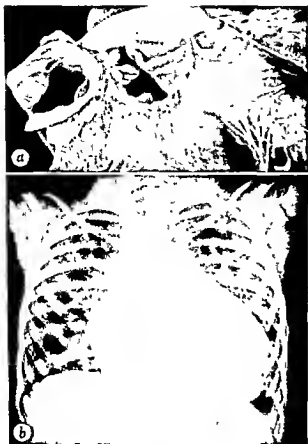


Figure VI-44 Ventricular septal defect and aortic insufficiency, in a 2-year-old boy.

a Aortic valve. The defect lies beneath the adjacent portions of the right and posterior (non-coronary) aortic cusps. Note fibrous thickening of cusps adjacent to defect. Dislocation of the aortic orifice causes some prolapse of the cusps and is probably mainly responsible for the aortic insufficiency. *b* Roentgenogram of thorax. In addition to evidence of pulmonary congestion from a large left-to-right shunt, the heart is enlarged because of dilatation of the left ventricle to which the aortic insufficiency contributed.

gresses of right-to-left shunts. In general, the larger the right-to-left shunt, the less likely are the pulmonary arterial and right ventricular pressures to fall to the desired levels as a result of closure of the defect. In infants, a large left-to-right shunt represents a formidable problem. On the one hand, such infants are in great danger of dying if the defect is untreated, on the other hand, they do not respond well to the major surgical treatment required to close the defect. As a temporary measure, the surgical production of pulmonary stenosis (Civin and Edwards, 1950; Muller and Dammann, 1952a and b) may be justified; if this prevents death in infancy it may be followed by a definitive operation for closure of the defect when

the patient is older and his general condition more favorable.

Developmental Basis

The various types of ventricular septal defects have different explanations for their genesis. Simplest to understand are defects of the muscular part of the inflow portion of the ventricular septum, which represent persistence of the interventricular communications in the developing heart (Winsatt and Lewis, 1918). (See Chapter II, page 50).

The common variety of ventricular septal defect, which lies inferior to the crista supraventricularis and inferior to the aortic valve, in the past has been termed *membranous ventricular septal defect*, the implication being that the defect results from deficiency in development of the membranous portion of the septum. Although this may explain the defects that are restricted to the normal territory of the membranous portion of the ventricular septum, it cannot explain defects that involve the territory of the muscular part of the ventricular septum. A more acceptable explanation for these defects is that the tissue that is to form the membranous portion of the ventricular septum fails to make union with the tissue of the muscular part of the ventricular septum. Even without deficiency in growth of tissue, simple failure of fusion would lead to an interventricular communication as the heart grows in size.

Defects lying above the crista supraventricularis and bordered above by the pulmonary and aortic valves involve tissue that is derived from the cono-truncal septum. These defects appear to represent deficiency in development of septal tissue of that area.

The rare defects that lie immediately beneath intact atrioventricular valves may be explained by failure of fusion between the atrioventricular endocardial cushions above and the muscular part of the ventricular septum below. Here again, a simple failure of fusion will produce a defect as the heart grows and as two tissues, which should have joined, are drawn away from each other.

Defects of the ventricular septum that allow communication between the left ventricle and

the right atrium, may be regarded as true defects of the membranous part of the ventricular septum. In the normal heart a portion of the floor of the right atrium is formed by membranous ventricular septal tissue.

Tucker and Kinney (1945) have described a defect in the outflow portion of the ventricular septum of the heart of a mother and that of her fetus.

VENTRICULAR SEPTAL DEFECT WITH PULMONARY STENOSIS

Small Defect

McCord and associates (1957) reviewed the hemodynamic spectrum of pulmonary stenosis combined with ventricular septal defect. If the ventricular septal defect is large, the direction of shunt depends principally on the degree of pulmonary stenosis. If the defect is small, the pulmonary stenosis becomes the dominant feature and the ventricular septal

defect is of minor importance, the behavior of the cardiovascular system being then essentially like that in hearts with an intact ventricular septum (Shumacker and Lurie, 1953, McGoon and Kirklin, 1958).

Large Ventricular Septal Defect (Tetralogy of Fallot)

In most cases in which a ventricular septal

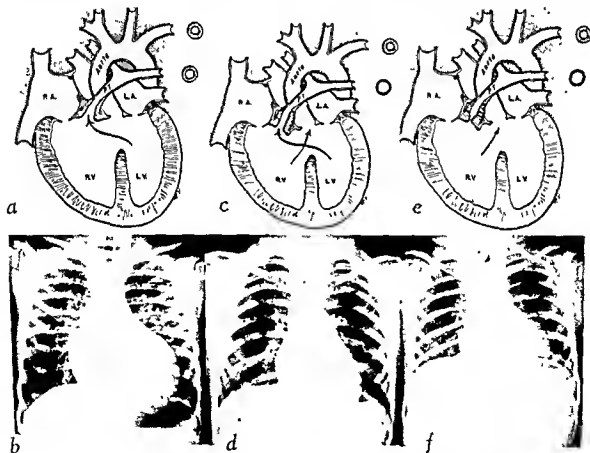


Figure VI-45. Diagrammatic representation of the intracardiac circulation in the anatomic tetralogy of Fallot with mild, moderate and severe pulmonary stenosis and roentgenograms of three illustrative cases. *a*. Mild pulmonary stenosis with only a left-to-right shunt. *b*. Roentgenogram of a 10-year-old child, representative of the condition shown in *a*. *c*. Moderate pulmonary stenosis with predominant left-to-right and small right-to-left shunt. *d*. Roentgenogram of a 7-year-old child, representative of conditions shown in *c*. *e*. Severe pulmonary stenosis with significant right-to-left shunt. *f*. Roentgenogram of a 3-year-old child, representative of the condition in *e*. The child also had a right aortic arch. (From Edwards, "Recent Concepts of the Functional Pathology in Ventricular Septal Defect," *Wisconsin Med. J.*, 56:481-485, 1957. Reproduced with permission.)



Figure VI-46. Anatomic tetralogy of Fallot with severe pulmonary stenosis. *a* The right ventricle and aorta have been opened, revealing the characteristic features of the anatomic tetralogy of Fallot. The sigmoidal subpulmonary outflow tract of the right ventricle is shown lying between the crista supraventricularis (C.S.) and the ventral wall of the right ventricle (R.V.). The open pulmonary trunk and pulmonary valve are shown in *b*. *b*. Subpulmonary outflow tract of the right ventricle and opened pulmonary valve and trunk. The thick endocardium of the subpulmonary tract of the right ventricle is evident. The tract lies between the crista supraventricularis (C.S.) and the ventral wall of the right ventricle (R.V.). In the inferior part of the tract, warty vegetations are attached to the endocardium wall. The pulmonary valve is bicuspid. *c*. Outflow tract of the right ventricle and opened pulmonary trunk in a case of tetralogy of Fallot with severe pulmonary stenosis. The outflow tract of the right ventricle, which lies between the crista supra-

defect is associated with pulmonary stenosis, the ventricular septal defect is large and, therefore, allows free communication between the two ventricles. In the past, the so-called tetralogy of Fallot was believed to have a consistent clinical picture. It is now evident, however, that patients with essentially the same anatomic cardiac defects may vary considerably in their functional and clinical manifestations (Figure VI-45). Thus, among patients having the malformation which anatomically may be designated as tetralogy of Fallot, the functional behavior of the cardiovascular system may vary as widely as in patients who have ventricular septal defect without pulmonary stenosis (McCord *et al.*, 1957).

Historical Aspects. According to Bennett (1946), Sandifort in 1777 was the first to give a clear description of the condition now known as the "tetralogy of Fallot." Fallot (1888) reported on the clinicopathologic correlation of the malformation in which pulmonary stenosis was severe. Willis (1948) reviewed accounts of this condition published during the eighteenth century and early nineteenth century, including those of William Hunter, Farre and Gintroc.

PATHOLOGIC ANATOMY

The anatomic tetralogy of Fallot consists of a large ventricular septal defect, obstruction to pulmonary blood flow (in the heart, at the pulmonary valve, or in the pulmonary trunk), ready communication of the aorta with both ventricles above the ventricular septal defect (so-called dextroposition of aorta), and a thick right ventricular wall. Hearts with this malformation have a striking abnormality of the crista supraventricularis (Figure VI-46). This structure normally (Edwards *et al.*, 1947) arches from the tricuspid ring toward the patient's left and toward the pulmonary valve. In the heart with an anatomic tetralogy of Fallot, the crista is more

ventricularis (C.S.) and the ventral wall of the right ventricle (R.V.), is narrow and has a sigmoidal shape brought about by the projection of the crista supraventricularis into the channel. The atretic pulmonary valve is illustrated in better prospective in Figure VI-48e.

vertical than normally and its lower aspect is not closely related to the tricuspid ring, but rather lies more to the left side, and is related to the anterior wall of the right ventricle between the ventricular septum and the tricuspid ring. Another difference is in the chordae which normally emanate from the adjacent portions of the anterior and septal leaflets of the tricuspid valve and insert into the ventricular septum at the papillary muscle of the conus; in anatomic tetralogy of Fallot, however, they insert to the right of the crista supraventricularis, frequently at the lower edge of the ventricular septal defect. Thus, instead of their normal close relation to the outflow tract of the right ventricle, they are related more closely to the origin of the aorta. Formerly it was thought that the ventricular septal defect in the anatomic tetralogy of Fallot was located in the membranous part of the septum. The membranous portion of the septum, however, may be present in its entirety or it may be identified as a rudimentary structure which protrudes into the space between the two ventricles. The ventricular septal defect lies posterior to the crista and more superiorly than in the usual variety of ventricular septal defect.

In ventricular septal defect without pulmonary stenosis, the ready communication of the aorta with the right ventricle in the anatomic tetralogy of Fallot is somewhat more striking than is the communication of the aorta with the right ventricle. The ventricular septal defect should be viewed, not as a true deficiency of ventricular septal tissue, but rather as a space located above the ventricular septum and just below the origin of the aorta from both ventricles.

Usually, the basis for impairment to pulmonary blood flow (Brock, 1949; Sellors and Belcher, 1950; Burke *et al.*, 1951; Berri *et al.*, 1952; Baffes *et al.*, 1953; Brinton and Campbell, 1953; Johns *et al.*, 1953) in tetralogy of Fallot is the narrow subpulmonary outflow tract of the right ventricle. This channel, which has been termed "the third ventricle," is bounded by the crista supraventricularis posteriorly, the anterior wall of the right ventricle anteriorly and the ventricular septum on the left. The caliber of this narrow tract varies.

In some instances it has essentially the same diameter throughout its course; more commonly the lowermost portion is the narrowest. Occasionally (Brinton and Campbell, 1953) there are two zones having about the same degree of stenosis in this tract. The lowermost region of the subpulmonary tract of the right ventricle has been termed the *ostium of the infundibulum*. In the past, instances of obstruction restricted to the ostium of the infundibulum have been separated from those of tetralogy of Fallot in which the entire tract showed some degree of narrowing (Figure VI-47).

When the obstruction to pulmonary flow is restricted to the lower portion of the ostium of the infundibulum, the infundibulum above the obstruction is usually fairly wide, and the pulmonary valve and pulmonary trunk are of normal width or sometimes wider than normal. The pulmonary valve then has three cusps whereas, in most cases of anatomic tetralogy of Fallot, the pulmonary valve is bicuspid (Koletsky, 1941; Figure VI-48a). Atresia of the subpulmonary tract of the right ventricle is rare (Figure VI-48b).

Next in order of relative frequency to infundibular stenosis, as a cause of major obstruction to pulmonary blood flow, is *stenosis of the pulmonary valve itself*. This stenotic valve (Edwards *et al.*, 1947) may be the point of greatest obstruction to the flow of blood between the right ventricle and the pulmonary trunk. Sometimes the barrier to pulmonary blood flow seems to be the result of a combination of stenosis of both the subpulmonary outflow tract and the pulmonary valve. Significant obstruction may occur at the pulmonary valve (Figure VI-48c and d) or there may be atresia of the valve (Figure VI-48e and f) caused either by fusion of the pulmonary cusps or by absence of a continuous channel between the right ventricular cavity and the pulmonary trunk. The pulmonary trunk is usually narrower than the aorta and narrower than normal, but may be of normal width or wider.

Least common among the causes of obstruction to pulmonary blood flow is *narrowing of the pulmonary trunk*. In most instances of tetralogy of Fallot, the pulmonary trunk is narrower than normal but is not the narrowest portion of the channel leading to the pulmonary arteries. Rarely the pulmonary trunk is stenotic (Chase, 1929; East and Barnard, 1938; Feldman and Snook, 1938; Sternberg *et al.*, 1947) or atretic and resembles a fibrous cord (Greenspon and Leaman, 1939; Miskall, 1945).

Anatomic tetralogy of Fallot with atresia of the



Figure VI-47. Stenosis of ostium infundibuli from a 47-year-old man, a patient of Cavin and Edwards (1930). *a*. The right ventricle and the pulmonary valve. Caudal to the pulmonary valve, the outflow tract of the right ventricle is narrowed by a fibrous collar. *b*. The opened pulmonary valve and cephalic portion of the right ventricular outflow tract. At the caudal portion of the tract is shown the unopened collar, constituting stenosis of ostium infundibuli. Functionally, this is classed as ventricular septal defect with mild pulmonary stenosis.

lower portion of the pulmonary trunk has been called "truncus arteriosus" by Taussig (1947*a* and *b*). Cooley and associates (1949) referred to this type of malformation as "pseudotruncus arteriosus" and, in so doing, adopted Taussig's designation. From a developmental point of view, however, the term "truncus arteriosus" for this condition should be avoided, the presence of a pulmonary trunk, even though it is atretic, and of an aorta is sufficient evidence that the truncus arteriosus has been partitioned.

In most instances of pulmonary atresia, the left and right pulmonary arteries are present and patent, rarely either the left or the right pulmonary artery is absent. Blalock (1948) noted, at operation or necropsy, absence of one of the pulmonary arteries in 9 of 610 patients operated upon for pulmonary stenosis. In anatomic tetralogy of Fallot, the left pulmonary artery is usually the one that is absent (Emanuel and Pattinson, 1956). A right aortic arch is present in about 60 per cent of these cases.

Constriction of the pulmonary trunk at its bi-

furcation, with involvement of the origins of its branches, is occasionally observed in patients with ventricular septal defect and pulmonary stenosis (Shumacker and Lurie, 1953; S ndergaard, 1954; Coles and Walker, 1956; Williams et al., 1957). S ndergaard suggested the term "coarctation of the pulmonary artery" for this condition, a view supported by Coles and Walker. It is not yet known whether the constriction is congenital or acquired and, for this reason, it is preferable to use the less definitive term, postcalcular stenosis of the pulmonary artery, proposed by Williams and associates.

Absence of the pulmonary valve is occasionally encountered (Case I of East and Barnard, 1938; Sternberg et al., 1947). Campeau and associates (1957) noted absence of the pulmonary valve, associated with a single coronary artery and a large ventricular septal defect but no pulmonary stenosis. In many instances of the anatomic tetralogy of Fallot, the pulmonary cusps may show peculiar excrescences representing focal concentrations of loose connective tissue. Because

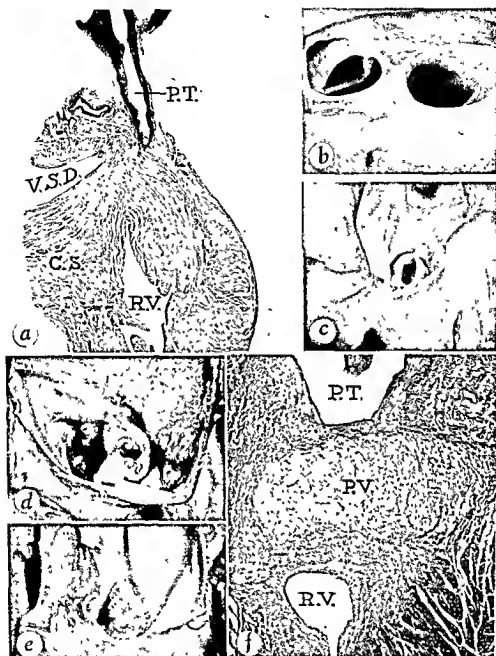


Figure VI-48. Varying causes of obstruction to the pulmonary blood flow. *a.* In serial sections of the heart and pulmonary trunk, no connection was found between the right ventricular cavity (R.V.) and the pulmonary trunk (P.T.). V.S.D. indicates ventricular septal defect, C.S., crista supraventricularis; R.V., right ventricular cavity. (E.L.G., X4.) *b.* Aorta and pulmonary trunk in cross section at the base of the heart. The pulmonary valve is bicuspid and is only mildly stenotic. *c.* Pulmonary valve from above, the pulmonary trunk has been opened longitudinally. The valve is bicuspid and stenotic. *d.* Pulmonary valve from above; the pulmonary trunk has been opened longitudinally. Severe pulmonary stenosis is present. *e.* Pulmonary valve from above, the pulmonary trunk has been opened longitudinally. The two cusps of the bicuspid pulmonary valve are fused to form an imperforate dome-shaped structure. *f.* One of a series of serial sections through the pulmonary trunk and outflow tract of the right ventricle. The pulmonary valve (P.V.) is anomalous and has no valvular structure. Instead, a plate of young connective tissue lies between the pulmonary trunk (P.T.) above, and the right ventricle (R.V.) below. (Hematoxylin and eosin; X30.)



Figure VI-49 Anomalous coronary arteries associated with anatomic tetralogy of Fallot. *a.* The right coronary artery does not arise as an independent vessel. Only one coronary artery, the left coronary artery (L.C.), is present. It has its usual branches, namely, the anterior descending (A.D.), the left circumflex (L.cir.) arteries, in addition, it gives rise to the right coronary artery (R.C.) which crosses the front of the outflow tract of the right ventricle on its way to the right atrioventricular sulcus. *b.* Absence of the origin of the left coronary artery. Only a single artery, the right coronary artery (R.C.), emerges from the aorta. From this vessel arise the left circumflex coronary artery (L.cir.) and a large branch which crosses the front of the outflow tract of the right ventricle (A.D.) on its way to the anterior interventricular sulcus. The right coronary artery itself continues directly into the right atrioventricular sulcus.

this appearance is most striking in hearts of newborn infants and is less often seen in older individuals, it may be that, with growth as tissue is incorporated in the valve cusps, some of the changes are effaced.

Usually the *aortic valve* is normal, having three well-formed cusps. Rarely the three cusps are of unequal size. Sometimes there are four cusps, three being essentially normal and the fourth, rudimentary. Histologically, the aortic wall is normal, but the wall of the pulmonary trunk is as thin as a vein, its media being thin and its elastic fibers often discontinuous (Heath *et al.*, 1958).

The *coronary arteries* arise from the aorta and frequently their ostia are located in anomalous positions with respect to the aortic sinuses. Occasionally one coronary artery may be absent. In Bach's case (1928) only the right coronary artery was present. In one specimen examined by the author, the ostium of the left coronary artery was stenotic but the vessel beyond this point was of normal caliber and the right coronary artery was normal, the wall of the left ventricle showed wide

areas of scarring, resembling a healed infarct. A large branch of the right coronary artery often descends along the anterior wall of the right ventricle in relation to its outflow tract, especially if atresia of the main left coronary artery is associated. Branches from the right coronary artery may proceed to the apex of the right ventricle or may anastomose with branches of the anterior descending coronary artery in the anterior aspect of the heart. The anomalous position of such a prominent branch from the right coronary artery must be recognized in performing corrective surgery, since it lies close to the usual site of right ventriculotomy. This is also the case when the right coronary arterial ostium is closed, and large collateral vessels from the left coronary artery cross on the anterior surface of the base of the right ventricle to reach the right atrioventricular sulcus (Figure VI-49).

A cardinal feature of the anatomic tetralogy of Fallot is increased *thickening of the right ventricular wall* which usually equals or exceeds that of the left ventricle. This is understandable since

the right ventricle shares with the left the function of supplying blood to the aorta. In this condition the right ventricle resembles that of the normal fetus in that the right ventricle and the left each acts as a systemic ventricle. Patten (1946) emphasized that the thick right ventricular wall in tetralogy of Fallot, therefore, represents persistence of a fetal relationship between the two ventricles. The chamber of the right ventricle may be of normal size, but often it is somewhat larger than that of the left ventricle. This enlargement is explained by the return of more blood through the systemic veins to the right side of the heart than is returned through the pulmonary veins to the left side of the heart. The enlarged and thickened right ventricle characteristically forms the cardiac apex (Pescatore *et al.*, 1939).

Gasul and associates (1949) reported the occurrence, in a girl aged 9 years, of atrial septal defect and enlargement of the left ventricle in association with tetralogy of Fallot; left axis deviation was demonstrated in the electrocardiogram during life. Cooley and associates (1949) reported that, in a boy aged 3 years and 8 months, the clinical and angiocardiographic findings were consistent with those of the anatomic tetralogy of Fallot, but the electrocardiogram showed left axis deviation. In a case reported by Taussig (1947b), the left ventricle was larger than the right. Paul and associates (1954) observed electrocardiographic evidence of left ventricular hypertrophy in a cyanotic infant who was thought to have atresia of the tricuspid valve. Subsequent examination revealed anatomic tetralogy of Fallot with pulmonary stenosis and enlargement of the left ventricle.

The *foramen ovale* often is valvular-competent and patent, but a true atrial septal defect is uncommon. The complex of patency of the *foramen ovale*, associated with the other features of the anatomic tetralogy of Fallot is sometimes referred to as the "pentology of Fallot."

INCIDENCE

In a study of 357 hearts with congenital malformations of the heart and great vessels at the Mayo Clinic, Fontana (1957) found 28 instances of the anatomic type of tetralogy of Fallot (8 per cent). Brinton and Campbell (1953) noted various types of congenital cardiac malformations in 55 necropsies in Cuy's Hospital during the years 1947 to 1950 and encountered 25 hearts with the tetralogy of Fallot. This relatively high

incidence may be explained by the relatively high percentage of patients with this condition who were seeking medical and surgical advice.

Ober and Moore (1955) studied malformations of the heart causing death in the neonatal period. They found the tetralogy of Fallot in 4 per cent, as compared with 15 per cent in the series of Abbott (1927). The relatively low incidence of 4 per cent in Ober and Moore's study is undoubtedly explained by the derivation of their material from a selected group of young persons. In general, patients with anatomic tetralogy of Fallot die at older ages than patients with many other cardiac malformations.

Among 49 persons with malformations of the heart in whom specific diagnoses were made at the Charity Hospital in New Orleans, 3 had the tetralogy of Fallot (Roberts, 1937).

SEX DISTRIBUTION

Of the 27 cases studied by Fontana (1957) in which the sex was known, 16 were males and 11 females. Of 25 cases of anatomic tetralogy of Fallot with pulmonary stenosis (no cases of pulmonary atresia) reported by Brinton and Campbell (1953), 11 were in males and 14 in females.

FUNCTIONAL AND STRUCTURAL EFFECTS

The essential functional disturbances of the tetralogy of Fallot with severe pulmonary stenosis have long been understood from correlated studies of the clinical and morphologic features (Fallot, 1888, Young, 1907).

Studies of cardiac catheterization, peripheral oxygen saturation, and angiocardiography (Grishman *et al.*, 1941; Sussman *et al.*, 1943; Eskildsen, 1944, Keith, 1948; Cooley *et al.*, 1949; Campbell and Hills, 1950; Holling and Zak, 1950; Keyes *et al.*, 1951; Lowe, 1953) have given broader understanding of the functional deviations.

The Fetal State. In normal fetal life, the two major systems of circulation are in free communication by way of the ductus arteriosus and, therefore, the existence of a large ventricular septal defect is basically of no consequence. In anatomic tetralogy of Fallot in which the pulmonary stenosis is severe, the reduction of flow from the right ventricle into the pulmonary trunk is compensated by the flow from the right ventricle into the aorta. In such cases it is probable that the direction of flow in the ductus arteriosus during fetal

life is from the aorta into the pulmonary trunk. In some patients with severe pulmonary stenosis, the ductus arteriosus may be absent or not identifiable by the time of birth. Such findings must be interpreted to represent, not failure of formation of the ductus arteriosus, but rather early obliteration, the channel having been used too little as a consequence of the associated malformations.

The Postnatal State. After birth, in hearts with large ventricular septal defects, the degree of obstruction to pulmonary flow becomes the determining factor in the behavior of the cardiovascular system (Selzer, 1951). Patients with the anatomic tetralogy of Fallot may be classified into three groups, depending on the degree of resistance to pulmonary flow compared to systemic flow, namely, those with (1) severe, (2) moderate and (3) mild pulmonary stenosis. One may assume that severe pulmonary stenosis or atresia is present when the resistance to flow through the stenotic channel is greater than the resistance to flow through the systemic circulation, moderate, when the resistance to flow through the tract leading to the pulmonary arteries is about the same as, or slightly less than, that in the systemic circulation, and mild, when resistance to flow through the stenotic channel is distinctly less than through the systemic circulation.

Severe Pulmonary Stenosis. An essential feature of the anatomic tetralogy of Fallot with severe pulmonary stenosis is that the right ventricle supplies blood to both the aorta and the lungs. Since the systemic systolic blood pressure is within normal limits (Baker *et al.*, 1949), the right ventricle, which shares with the left ventricle the function of supplying blood to the aorta, must exert systemic pressure. Thus the condition resembles that in the normal fetus, in which both ventricles supply blood to the systemic circulation. In the fetus the right ventricular wall is as thick as the left, because the two ventricles exert similar pressures (Hamilton *et al.*, 1950). In anatomic tetralogy of Fallot, the thickness of the right ventricle is explained in a similar manner (Patten, 1946). Catheterization studies have demonstrated right ventricular hyper-

tention. Moreover, simultaneous readings show that the systolic pressure of this chamber is like that in the aorta (Bing *et al.*, 1947; Dexter *et al.*, 1947; Lagerlöf *et al.*, 1949). The pressure within the major pulmonary arteries is understandably low, while the characteristic difference in pressure between the right ventricle and the pulmonary trunk is explained by the interposition of the zone of stenosis.

Dow and associates (1950) reported that, in the tetralogy of Fallot, pressure tracings suggested stenosis both of a valvular orifice and of the lower portion of the subpulmonary tract. The basis for this interpretation was that the systolic pressure in the outflow tract of the right ventricle was greater than that in the pulmonary trunk and less than that in the main portion of the right ventricle. The volume of pulmonary blood flow is less than normal. The right-to-left shunt from the right ventricle to the aorta may be demonstrated by angiocardiographic studies and by dye-dilution studies (Swan *et al.*, 1953) such as a short circulation-time from arm to tongue (Gordon *et al.*, 1953). Quantitation of the degree of right-to-left shunt is also possible by the dye-dilution method.

Systemic arterial destruction in the anatomic tetralogy of Fallot with severe pulmonary stenosis (Burchell, 1947; Campbell, 1948) is dependent in a large measure on two closely interrelated factors: (1) a shunt of venous blood from the right ventricle into the aorta, and (2) diminished pulmonary blood flow. In general, the greater the degree of pulmonary stenosis, the more blood will flow from the right ventricle into the aorta. At the same time, it must be realized that the blood which flows from the left ventricle into the aorta has passed through the lungs, having entered the lungs through the pulmonary trunk and collateral channels. The gross barrier to pulmonary blood flow is fixed at a given time. All other factors being equal, the amount of blood which will flow to the lungs through the area of pulmonary stenosis will depend on the level of the resistance to systemic blood flow.

In patients with the anatomic tetralogy of Fallot and severe pulmonary stenosis, a severe fall in

systemic blood pressure is accompanied by a precipitous decrease in the oxygen saturation of the peripheral arterial blood (Burchell and Wood, 1949; Hamilton *et al.*, 1950). These reactions probably depend on greatly altered resistance to systemic flow. With the changes in systemic blood pressure induced by administration of tetraethylammonium ion and phenylephrine hydrochloride (neosynephrine hydrochloride), Burchell and Wood observed no significant change in the oxygen saturation of the arterial blood. Moreover positive-pressure breathing failed to cause a decrease in oxygen saturation of the arterial blood, although this procedure might be expected to raise the resistance to pulmonary blood flow.

During exercise, patients with this defect characteristically have intensification of cyanosis and a fall in the oxygen saturation of the peripheral arterial blood (Rutledge and Adams, 1947; Montgomery *et al.*, 1948). This phenomenon is probably dependent on several factors, including increased uptake of oxygen by the tissues, increased cardiac output, decreased resistance to systemic flow, and possibly increased resistance to pulmonary blood flow (Burchell *et al.*, 1950). Angiocardiographic studies indicate that the subpulmonary outflow tract of the right ventricle narrows with ventricular contraction (Boesen *et al.*, 1956).

Endocardial Thickening of the Subpulmonary Tract is the result of formation of collagen and elastic tissue (Figure VI-50) and adds to the irregularity of the contour of the channel and to an accentuation of the obstruction. These deposits may represent the reaction to the trauma of the blood which flows through the stenotic region. Brock (1949) has emphasized that the secondary changes in the lining of the subpulmonary tract make the channel more rigid and progressively more stenotic. In addition to endocardial thickening at the site of the major obstruction, secondary thickenings also occur beyond this region. The latter are thought to result from the trauma of impact of jets of blood originating at the primary site of obstruction (Figure VI-50d and e).

Collateral Supply to the Lungs. One of the consequences of severe obstruction to pulmonary blood flow is the presence of enlarged collateral vessels to the lungs (Figure VI-51). This system seems to develop with

increasing age of patients. Thus, Bing and associates (1947) found that young patients had little evidence of blood flow through the lungs beyond that which flowed through the pulmonary trunk, while older patients had evidence of collateral circulation. This observation, in general, supports the concept that the better the collateral circulation to the lung, the more likely the patient is to survive severe obstruction to pulmonary blood flow.

The Bronchial Arteries are important collateral pathways to the lungs in pulmonary stenosis or atresia (Stölker, 1864; Weiss, 1875; Middendorp, 1886; East and Barnard, 1938; Greenspon and Leaman, 1939; Talbott *et al.*, 1941; Sternberg *et al.*, 1947; Allanby *et al.*, 1950). Christeller (1917) has given an excellent review of the subject. Graphic demonstration of the rich collateral vascular supply to the lungs furnished by the bronchial and other mediastinal arteries has been presented (Hales and Liebow, 1948; Britton *et al.*, 1950; Collister *et al.*, 1953) by means of vinylite corrosion-casts of the lungs. It should be emphasized that in most cases of anatomic tetralogy of Fallot with pulmonary atresia, the collateral vessels are the sole channels by which blood comes to the lungs. Moreover, in many cases of severe pulmonary or subpulmonary stenosis, the lungs receive more blood from the collateral vessels than they do by the normal pathway. The dilated bronchial arteries may distort the esophagus (Taussig, 1947b; Campbell and Gardner, 1950). This feature may be demonstrated roentgenographically (Cooley *et al.*, 1949).

Case 1 of Taussig (1947b) was a 4-months-old infant with pulmonary atresia and greatly dilated bronchial arteries. Absence of the ductus arteriosus was disclosed at necropsy. This suggests that collateral pathways had developed during fetal life, since they were the only avenues for passage of blood to the lungs, and must have been in effective operation when the umbilical cord was ligated at birth; otherwise, life would have failed at that time. Kintner and Kintner (1951) described collateral supply to the lungs from a coronary artery.

One should suspect that a collateral artery communicates with one of the major pulmonary arteries if, during cardiac catheterization, the oxy-

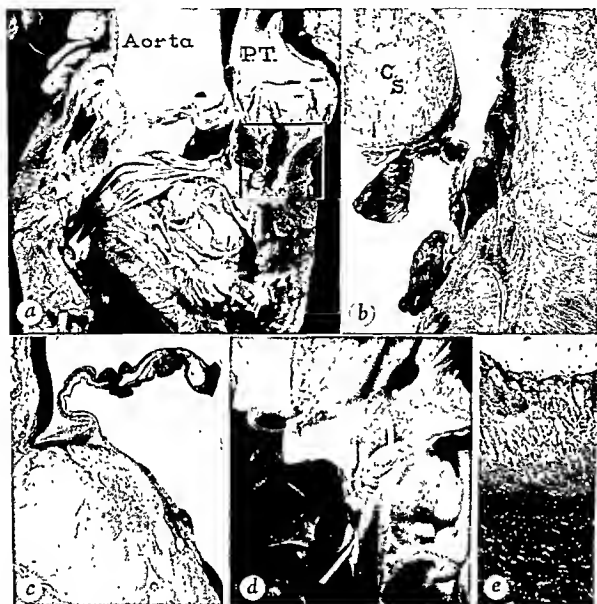


Figure VI-50 Sites of endocardial and intimal fibrous thickening in anatomic tetralogy of Fallot. *a*. Right ventricle. Within the lower portion of the subpulmonary outflow tract is a zone of marked endocardial fibrous thickening. *C.S.* indicates crista supraventricularis, and *P.T.*, pulmonary trunk. *b*. High-power illustration of area within square in *a*. The marked endocardial thickening is shown. (EL-vG, X4) *c*. Associated infundibular stenosis. Upper portion of subpulmonary tract and of pulmonary valve. There is irregular fibrous thickening of endocardium of right ventricle and of pulmonary valvular tissue. (EL-vG, X3.) *d*. Pulmonary trunk and outflow tract of right ventricle. The probe extends from the right ventricular cavity through the infundibulum and appears in the pulmonary trunk above the pulmonary valve which is bicuspid. At the upper end of the probe, there is thickening of wall of pulmonary trunk which is illustrated in *e*. *e*. Jet lesion on pulmonary trunk which is illustrated grossly in *d*. (EL-vG; X90.)

gen saturation of the blood within the pulmonary artery is found to be significantly higher than in the right ventricle. It is obvious that such flow into a major pulmonary artery may complicate the procedure of extracorporeal circulation, for a considerable portion of the blood perfused into the systemic arterial system will appear in the operative field either through the pulmonary valve

or through the ventricular septal defect after flowing through the pulmonary circuit into the left side of the heart. The author has observed unusual collateral pathways in 3 cases of anatomic tetralogy of Fallot with severe pulmonary stenosis. In one, an accessory artery extended to the right lower pulmonary artery from the abdominal aorta. In the other two cases, wide bronchial arteries

communicated with the right pulmonary arteries at the pulmonary hilus (Figure VI-51c and d).

Tejada Valenzuela and associates (1954) reported, in anatomic tetralogy of Fallot with pulmonary atresia, that an anomalous artery from the abdominal aorta supplied the lower half of the right lung, while the upper half of the right lung was connected normally with the pulmonary arteries. In addition, the ductus arteriosus was widely patent.

It is recognized that persistent patency of

the ductus arteriosus produces the same functional effects as in the type of collateral arteries mentioned. In most cases of tetralogy of Fallot, the ductus arteriosus is patent during the first 2 weeks after birth, and then undergoes closure, despite the desirability of continued patency.

The Intrapulmonary Arteries. The structure of the smaller intrapulmonary arteries and arterioles is within limits of normal (Tosetti

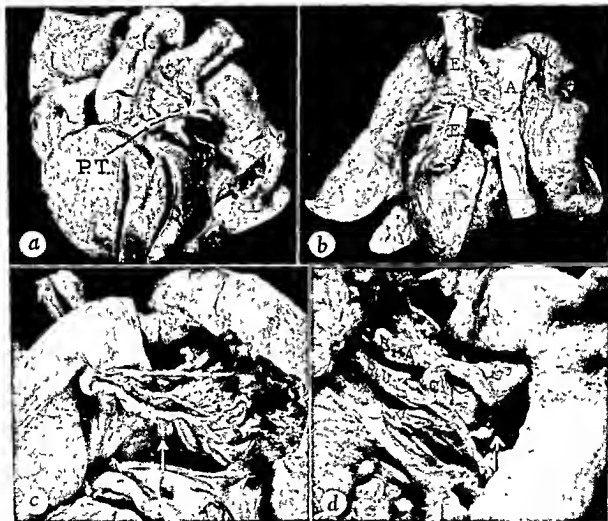


Figure VI-51. Collateral vessels to lung. *a.* Anterior view of thoracic organs from a 3-week-old child with ventricular septal defect and pulmonary stenosis. There is a right aortic arch. The pulmonary trunk (P.T.) is very narrow and continues as the left pulmonary artery. The right pulmonary artery is absent. Bronchial arteries in this case are illustrated in *b.* *b.* Posterior view of thoracic organs of specimen illustrated in *a.* The aorta (A.) lies to the right of the esophagus (E.). Wide bronchial arteries originate from the descending aorta and proceed to each lung. A large branch to the left lung is seen crossing behind the esophagus. *c.* Posterior view of hilum of the right lung and right-sided descending aorta from a 14-month-old child with ventricular septal defect and pulmonary atresia. A series of large bronchial arteries arise from the anterior aspect of the upper descending aorta and extend to the right lung. The vessel above the point of arrow courses inferior to the right bronchus and is seen in better perspective in *d.* *d.* At the point of the arrow, the bronchial artery (seen at the point of arrow in *c*) crosses in front of the right bronchus and makes gross connection (C.) with the upper branch of the right pulmonary artery (R.U.) as well as crossing directly (Br.A.) into the hilum of the right lung.

et al., 1953; Dammann and Ferencz, 1956; Edwards, 1957). The walls are not thickened as in large ventricular septal defect without pulmonary stenosis.

Rich (1948) reported a high incidence of thrombi of varying ages, including completely organized thrombi, within the intrapulmonary arterioles. This observation has been confirmed (Hales and Liebow, 1948, Tosetti *et al.*, 1953). The reason for development of pulmonary arteriolar thrombi is not clearly evident, though they may result from polycythemia. The possibility of emboli from vegetations occurring in the outflow tract of the right ventricle must also be considered. These changes do not affect to any measurable degree the resistance to pulmonary flow. In many cases which the author has studied, no occlusive arteriolar lesions were found.

Moderate and Mild Pulmonary Stenosis. Selzer and Carnes (1953) emphasized the role of pulmonary stenosis in regulating blood flow when a large ventricular septal defect is present.

The function of hearts with the anatomic tetralogy of Fallot but only mild or moderate pulmonary stenosis differs from that of hearts with anatomic tetralogy of Fallot and severe pulmonary stenosis. In hearts with mild pulmonary stenosis, the striking feature is the left-to-right shunt. In such cases some responsibility for the regulation of blood flow rests on the pulmonary arterioles and small arteries which may show medial hypertrophic changes exactly as in the case of a large ventricular septal defect without pulmonary stenosis (Edwards, 1957). If the pulmonary stenosis is moderate, the functional characteristics are those of a significant left-to-right shunt and a mild right-to-left shunt. The functional features of such a heart may be simulated in the creation of pulmonary stenosis as a palliative procedure (Muller and Dammann, 1952) in patients with large ventricular septal defects and large left-to-right shunts without pulmonary stenosis.

Blount and associates (1955) have pointed out that left-to-right shunt may occur in ventricular septal defect with pulmonary stenosis when the degree of pulmonary stenosis is less than usual. Other writers have also described such cases

(Deuchar and Zak, 1952; Broadbent *et al.*, 1953; Rudolph *et al.*, 1954; Bashour and Winchell, 1955; Eldridge and Hultgren, 1955; Rowe *et al.*, 1955).

CLINICAL FEATURES

The clinical picture in pulmonary stenosis with large ventricular septal defect depends principally on the degree of pulmonary obstruction.

Severe Pulmonary Stenosis. The clinical features of severe pulmonary stenosis or pulmonary atresia have been described in a number of references (Brown, 1945; Green, 1945; Humphreys, 1947; Taussig, 1948; Wood, 1950; Gibson, 1952; Wells, 1952; Campbell and Deuchar, 1953). The predominant sign is cyanosis which is a reflection of the significant desaturation of the systemic arterial blood. In pulmonary atresia the cyanosis may be noted at birth while in many cases of pulmonary stenosis, the appearance of this sign is delayed. At times it appears at or shortly after birth; less often, it may not become apparent until childhood; and rarely, not until adolescence (Gasul *et al.*, 1957). Cyanosis, when present, is often accentuated by physical exertion; it is associated with clubbing of the digits and polycythemia. *Squatting* has often been noted in these patients. During this act, the oxygen saturation of the systemic arterial blood rises (Burchell, 1950). Patients with cyanosis may have fainting spells which are related to increased magnitude of the right-to-left shunt (Burchell, 1950). A systolic murmur may be generated at the stenotic subpulmonary tract (Reinhold and Nadas, 1954). Absence of such a murmur may suggest pulmonary atresia.

Cyanosis commonly is intensified at the time of adolescence. With growth of the body, the actual size of the stenotic tract leading to the pulmonary artery does not change much, but the volume of cardiac output increases, resulting in delivery of a greater volume of right ventricular blood to the aorta. In addition, with progressing age, as the endocardium of the right ventricular infundibulum shows progressive fibrous thickening (Figure VI-50), the tract leading to the pulmonary trunk may become narrower. Gasul and associates (1957) noted that some cyanotic patients who

presented evidence of ventricular septal defect and pulmonary stenosis had not been cyanotic on earlier examinations and had shown little, if any, evidence of pulmonary obstruction. The probable explanation is that in such patients the pulmonary stenosis was relatively mild during early life when the cardiac output was relatively small and the size of the infundibulum caused little obstruction. As the body grew and cardiac output increased, with the infundibulum remaining the same size, the orifice then became relatively narrower and, therefore, a right-to-left shunt appeared. *Retardation of body growth* has been noted (Harada, 1951, Adams *et al.*, 1954).

Among the *roentgenographic features* in the anatomic tetralogy of Fallot with severe pulmonary stenosis (Dry *et al.*, 1948; Baker *et al.*, 1949, Grob and Rossi, 1949, Keyes *et al.*, 1951, Downing, 1952, Gasul and Warnick, 1952, Wittenborg

and Neuhauser, 1955). The most consistent finding is increased radiance of the lungs, a manifestation of diminished pulmonary blood flow. While classically the pulmonary arterial segment is concave, in many cases this feature is not evident. If a concavity is present, the associated round apical shadow gives the heart the contour of a wooden shoe (*cœur en sabot*). *Angiocardiographic studies* give evidence of the right-to-left shunt between the right ventricle and the aorta, in that early filling of the aorta occurs simultaneously with filling of the narrow pulmonary arterial tract. In patients with severe pulmonary obstruction, cyanosis may be absent if the bronchial arterial flow is great. The author observed a patient who had roentgenographic signs of a narrow pulmonary trunk but evidence of excessive pulmonary flow. The patient was not cyanotic, having at rest an oxygen saturation of

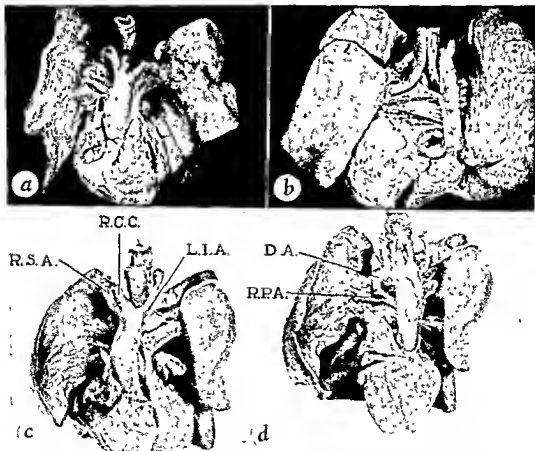


Figure VI-52 Anatomic tetralogy of Fallot with right aortic arch. *a.* The arch of the aorta passes ventral to the root of the right lung. *b.* Posterior view of thoracic organs. After the arch of the aorta has passed ventral to the root of the right lung, the upper part of the descending aorta remains on the right. (Figures *a* and *b* were prepared from the heart of a girl 7 years of age.) *c.* The aortic arch is on the right side. Its branches are reversed as compared to normal. The first branch is the left innominate artery (L.I.A.), the second, the right common carotid (R.C.C.); and the third, the right subclavian artery (R.S.A.). *d.* The arch is viewed from the right side. The ductus arteriosus (D.A.) runs between the right pulmonary artery (R.P.A.) and the aortic arch. (Figures *c* and *d* were prepared from a female infant 22 days old.)

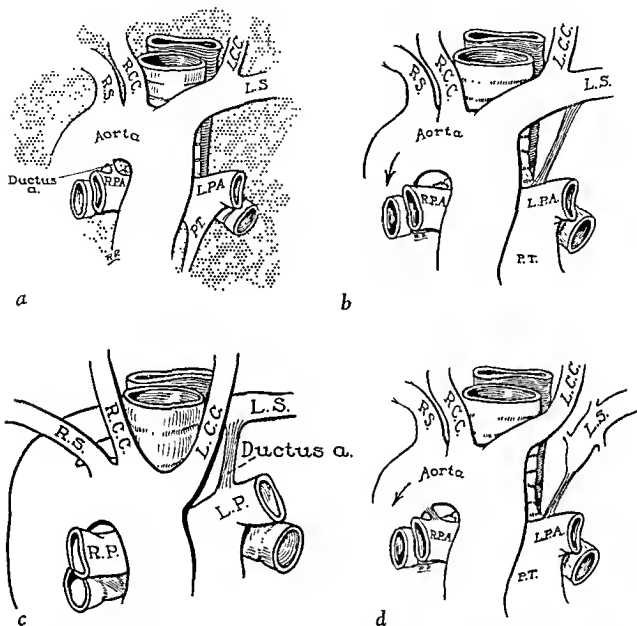


Figure VI-53 Types of right aortic arch encountered in anatomic tetralogy of Fallot. Abbreviations on pictures are evident. *a.* Branches of arch are mirrored image of the normal. In the case illustrated, a ductus arteriosus was present on the right side. In some instances of this aortic malformation, no ductus arteriosus is present on either side. In other instances, it is present on the left, as in *b.* *b.* Right aortic arch with mirrored image of branches of arch. The ductus arteriosus runs between the left pulmonary artery and the base of the left subclavian artery. *c.* Right aortic arch, with left subclavian artery arising directly from the aorta as its fourth branch. After passing behind the esophagus, the left subclavian artery receives the ductus arteriosus the lower portion of which is attached to the left pulmonary artery. Figure VI-54 is a roentgenogram from a case of this type. *d.* Right aortic arch in which the left subclavian artery does not connect with the aorta but, instead, takes origin from the left ductus arteriosus. In the case illustrated, a ductus arteriosus is present on each side, as in the case of Ghon (1908).

arterial blood of about 90 per cent. Functional studies indicated a severe degree of pulmonary stenosis as well as a greatly increased collateral blood supply to the lungs. The clinical picture in such a patient is apparently paradoxical, since cyanosis is absent despite the presence of severe pul-

monary stenosis. The electrocardiogram indicates right ventricular hypertrophy (Joly *et al.*, 1952).

Mild or moderate pulmonary stenosis. In pulmonary stenosis of mild or moderate degree, outward signs may be absent or the

patient may even suffer from the effects of the left-to-right shunt. If the latter case, the clinical features resemble those of patients having large ventricular septal defect without pulmonary stenosis. A precordial systolic murmur and thrill may be elicited. Cyanosis is absent in mild pulmonary arterial obstruction. In moderate pulmonary stenosis, cyanosis may be evident only on exercise. At times this sign may not be apparent to the eye, while instrumental studies will reveal mild degrees of arterial oxygen desaturation.

ASSOCIATED CONDITIONS

Malformations of Aortic Arch. Usually in the tetralogy of Fallot, the aortic arch and descending aorta are in normal location. In about a fifth to a fourth of the cases, however, the aortic arch is on the right side. The association of a right aortic arch with the tetralogy of Fallot is at times referred to as "Corvisart's disease" (Corvisart, 1818).

Blalock and Bahnson (1948) reported that a right aortic arch was present in approximately 140 of 610 patients operated upon for congenital pulmonary stenosis, most of whom had tetralogy of Fallot. Dammann and associates (1949) found a right aortic arch in 28 of 108 patients (26 per cent) operated upon for cyanotic congenital cardiac disease. Baker and associates (1949) reported 14 instances of right aortic arch among 50 patients operated upon for pulmonary stenosis; the great majority of the 50 patients had tetralogy of Fallot. When a right arch is present, the upper portion of the descending aorta also is usually on the right side (Figures VI-52 and VI-53a and b). In the lower part of the thorax, at about the level of the eighth thoracic vertebral body, the aorta then deviates to the left and leaves the thorax through the aortic hiatus of the diaphragm (Edwards, 1948). When the aortic arch is on the right side, the branches of the arch are usually reversed (Figures VI-52c and d and VI-53a and b). The first branch is an innominate artery from which the left common carotid and left subclavian arteries arise, the second branch of the arch is the right common carotid artery, and the third, the right subclavian artery. In variations of this pattern, the one in which four branches arise directly from the right aortic arch is probably most common. The first of these is the left com-

mon carotid artery; the second, the right common carotid, the third, the right subclavian artery; and the fourth, the left subclavian artery (Figure VI-53c). In this respect, the aortic arch and its branches form a mirrored image of that common malformation in which the right subclavian artery arises as the fourth branch of an otherwise normal aorta. (See Section on Malformations of the Aortic Arches, page 467.) When the left subclavian artery arises as the fourth branch of the right-sided aorta, it passes behind the esophagus to reach the left arm. The anomalous subclavian artery may then compress the esophagus and, at times, cause dysphagia, its presence may be detected on roentgenography (Figure VI-54).

While the upper portion of the descending aorta is usually on the right side when the aortic arch is on the right, in a relatively small number of cases the right arch crosses the midline behind the esophagus to join the upper portion of the descending aorta on the left side of the thorax (Brown and Morris, 1951).

Double aortic arches may be present occasionally. Blalock and Bahnson (1948) found one example of this aortic malformation in the 610 cases which they reported. Harris and Whitney (1927) encountered this malformation in a peculiar form. Of the two aortic arches, the one on the right side was much wider. In spite of a left-



Figure VI-51. Roentgenogram showing compression of esophagus by a vascular ring of type illustrated in Figure VI-53c. From a 4-year-old boy with the anatomic tetralogy of Fallot and severe pulmonary stenosis.

sided ductus arteriosus, the upper portion of the descending aorta was on the right side of the body. Paul (1948) described a left aortic arch with a right descending aorta in two cases in which operation was performed for the tetralogy of Fallot.

Among 56 hearts with anatomic tetralogy of Fallot which the author has examined, 10 were associated with a right aortic arch and one with double aortic arch. In 2 of the cases of right aortic arch, the left subclavian artery arose as the fourth branch of the aorta and was attached to the left ductus arteriosus after the subclavian artery had reached the left side of the body. In 1 case of right aortic arch, the left subclavian artery did not have any connection with the aorta but, instead, communicated at its origin with a narrow left patent ductus arteriosus (Figure VI-53d). The vascular connections were like those in the case of Ghon (1908), except that in Ghon's case there were bilateral ducti arteriosi. In another case in which the aortic arch was on the left side, the right subclavian artery arose as a fourth branch of the aorta and crossed to the right side of the body behind the esophagus.

Ductus Arteriosus. When the aortic arch is on the left side, the ductus arteriosus also is almost always on that side. When the aortic arch is on the right side, the ductus arteriosus may take one of two positions. It may run between the right pulmonary artery and the aortic arch, inserting into the arch just beyond the origin of the right subclavian artery (Figure VI-52d), or it may extend from the left pulmonary artery either to the left subclavian artery or to the left-sided innominate artery.

Blalock and Bahnson (1948) found that, when a right aortic arch was associated with tetralogy of Fallot, the ductus arteriosus was usually a left-sided structure inserting into either the left subclavian or the left innominate artery (Figure VI-53b). In Case 3 of Dexter and associates (1947), a boy of 10 years had the tetralogy of Fallot and evidence, clinically and on catheterization, of a right aortic arch associated with a right-sided descending aorta and a patent ductus arteriosus. The murmur of the patent ductus was more prominent over the aortic region than over the pulmonary, suggesting that the ductus entered the right pulmonary artery rather than the left. A left-sided ductus, however, was represented diagrammatically in their paper.

Absence of Ductus Arteriosus. Inasmuch as the aorta during fetal life is in free communication with the right ventricle, the ductus may be used little as a channel for bringing blood from the right side of the heart to the aorta. It may atrophy during fetal life and so be unidentifiable at the time of birth.

The writer has observed several such cases in each of which the aortic arch and upper portion of the descending aorta were on the right side (see also Myers and Keith, 1926). Taussig (1947b) reported an instance of atresia of the lower portion of the pulmonary trunk in which no tissue of the ductus arteriosus could be found at necropsy. Several instances of absence of the ductus arteriosus are listed in the review of Stoller (1864) on pulmonary stenosis.

Patency of the ductus arteriosus is uncommon (Miskall, 1945; Dexter *et al.*, 1947). When a patent ductus is present, it acts as an important collateral channel for blood to flow from the aorta to the pulmonary arterial system. In most patients with the tetralogy of Fallot who live beyond infancy to childhood or adult life, there is another well-developed system of collateral vessels which arise chiefly from the bronchial arteries.

Other Associated Conditions. In 1 of 56 cases of anatomic tetralogy of Fallot, the author observed a second ventricular septal defect which was located in the inflow portion of the ventricular septum. In still another case, the pulmonary valve was absent. A persistent left superior vena cava was observed on one occasion. In 2 cases mitral atresia was associated with anatomic tetralogy of Fallot. In 1 of these, an additional anomalous connection of the right pulmonary veins was present and in the other, there was also atresia of the larynx. Two patients, each showing a ventricular septal defect and infundibular stenosis, also had the atrial septal and atrioventricular valvular malformations which could be classified as persistent common atrioventricular canal. In 1 patient in whom the usual pulmonary veins were identified as connecting with the left atrium, a small accessory pulmonary vein from the upper lobe of the left lung was connected with the left innominate vein. A tracheoesophageal fistula was associated in 1 patient having a right aortic arch.

Of special importance is the uncommon phenomenon of atresia or stenosis of one of the coronary arteries. The author has examined a case of anatomic tetralogy of Fallot and atresia of the right atrial ostium of the coronary sinus, in which the coronary sinus communicated with the left

atrial cavity. (See section on Anomalies of Coronary Sinus, page 431.)

DIFFERENTIAL DIAGNOSIS

Among patients having a *small ventricular septal defect* with pulmonary stenosis, the major condition to be considered is ventricular septal defect with intact ventricular septum.

The differential diagnosis of a large ventricular septal defect with pulmonary stenosis requires consideration of many conditions. Patients with severe pulmonary stenosis or pulmonary atresia have cyanosis. If cyanosis is present, the conditions that must be ruled out include transposition of the great vessels, persistent truncus arteriosus with pulmonary stenosis, single ventricle with pulmonary stenosis, tricuspid atresia with pulmonary or subpulmonary stenosis, ventricular septal defect without pulmonary stenosis but with severe occlusive lesions in the intrapulmonary arteries and arterioles, single ventricle without pulmonary stenosis but with occlusive lesions in the muscular arteries and arterioles of the lungs, Ebstein's malformation of the tricuspid valve, and pulmonary arteriovenous fistula with cyanosis.

In patients with a *large ventricular septal defect* and mild or moderate pulmonary stenosis, conditions to be considered are those having a large left-to-right shunt. These include large ventricular septal defect without pulmonary stenosis and without occlusive lesions of the pulmonary vessels, single ventricle without pulmonary stenosis, tricuspid atresia without pulmonary stenosis, the usual variety of persistent truncus arteriosus, and patent ductus arteriosus with left-to-right shunt.

PROGNOSIS

The following discussion on prognosis, survival, and complications pertains to patients who were not treated surgically. Some of the factors discussed are modified by an anastomotic operation and are eliminated by a corrective one.

In 1927, Abbott reviewed 97 cases of tetralogy of Fallot. Among 73 patients in whom pulmonary stenosis was present, the highest age at the time of death was 28 years, the average being 10.8 years; among 24 who had pulmonary atresia, the greatest length of life was 13 years and the

average age at death was 3.4 years. The shorter survival in patients with atresia, as compared with those exhibiting pulmonary stenosis, is probably related to the lesser degree of collateral blood supply to the lungs in the young as contrasted with older patients. In patients with atresia, a patent ductus arteriosus may be an important collateral channel during the first few weeks after birth. When the ductus closes, the other collateral pathways may supply blood to the lungs in amounts insufficient to maintain life. In patients who have pulmonary stenosis, the existing arterial channel to the lungs, though narrow, may be adequate to maintain life until such time as the collateral vessels develop to carry significant amounts of blood to the lungs.

A number of authors have reported unusually long survival of patients with the anatomic tetralogy of Fallot without surgical treatment (White and Sprague, 1929, survival for 59 years; Feigin and Rosenthal, 1943, survival for 53 and 43 years; Middleton and Ritchie, 1947, 45 years; Volini and Flaxman, 1938, 41 years; Middendorp, 1886, 33 years; East and Barnard, 1938, 33 years; Perlman and Meyer, 1945, 32 years; and Bach, 1928, 30 years). Long survival may sometimes indicate a relatively mild pulmonary stenosis, as in the case of stenosis of the infundibular ostium associated with ventricular septal defect, reported by Civin and Edwards (1950; Figure VI-47).

COMPLICATIONS

The causes of death include pneumonia, congestive cardiac failure, subacute bacterial endocarditis, cerebral thrombosis, and cerebral abscess. In some cases, the cause of death cannot be demonstrated anatomically (Ash and Harshaw, 1939). Some patients, particularly children, may die during a characteristic attack of intensified cyanosis and unconsciousness, the probable immediate cause of death being cerebral anoxia.

The complication of *pneumonia* is serious for the patient with tetralogy of Fallot for two reasons: (1) Even a small reduction of functioning pulmonary parenchyma may cause increased hypoxia; (2) peripheral vasodilatation, with accompanying decreased resistance to systemic flow, may tend to increase the shunt of venous blood from the right ventricle to the aorta.

Congestive cardiac failure may develop in patients who survive to adult life (Feigin and Rosenthal, 1943, Middleton and Ritchie, 1947), but

apparently is not a prominent cause of death during childhood or adolescence.

Bacterial endocarditis is a frequent complication, particularly among patients who survive childhood. Gelfman and Levine (1942) noted bacterial endocarditis as a complication in 12.5 per cent of patients of all ages with the tetralogy of Fallot, and in 29 per cent of those who were 2 years of age or older. The endocarditis usually involves the right side (tricuspid valve, Perlman and Meyer, 1945, wall of subpulmonary outflow tract of right ventricle, Dustin and Lambert, 1942; pulmonary valve, Leadingham, 1936). In each of the cases cited the patient was 15 years of age or older at the time of death.

Cerebral thrombosis is probably best explained as a result of the polycythemia which is a characteristic finding in patients with the anatomic tetralogy of Fallot and severe pulmonary obstruction (Berthrong and Sabiston, 1951). Cerebral infarction may occur in the absence of thrombosis.

Cerebral abscess may develop in the absence of inflammatory disease of the heart. The condition is encountered in about 4 or 5 per cent of all cases of major congenital malformations of the heart and great vessels. Classically it is associated only with hearts in which a venous arterial shunt is possible.

The complication is explained as follows. Every person may have bacteremia from time to time, particularly in the presence of an infectious process such as tonsillitis or nasopharyngitis. Ordinarily, organisms entering the peripheral venous blood pass through the lungs and are filtered out of the blood stream. If, however, a venoarterial shunt exists, some venous blood carrying bacteria bypasses the lungs and flows into the systemic circulation without the benefit of the filtering action of the lungs. The peculiar tendency for infection to localize in the brain is not completely understood (Robbins, 1945). Since the tetralogy of Fallot with pulmonary obstruction is the most common malformation characterized by a venoarterial shunt, in which the chances for a relatively long survival are good, it is understandable why cerebral abscess is commonly encountered. In about half of the patients with the syndrome of cerebral abscess and congenital cardiac disease, the cardiac malformation is pulmonary stenosis with ventricular septal defect (Rabinowitz *et al.*, 1932; Wechsler and Kaplan, 1940; Hanna, 1941; Robbins, 1945; Cates *et al.*, 1947; Maronde, 1950, Sancetta and Zimmerman, 1950). Usually the abscess is solitary, less often multiple

(Sancetta and Zimmerman, 1950). Among patients in whom an abscess of the brain was recognized clinically (Sidenberg *et al.*, 1946; Smolik *et al.*, 1946; Hand, 1947; Arana Iniguez *et al.*, 1950; Beller, 1951; Cohen *et al.*, 1951; Green and Nadas, 1954), 4 were cured of the abscess by appropriate surgical treatment.

Some investigators still adhere to the concept that *pulmonary tuberculosis* is a common complication of tetralogy of Fallot (Buckingham and Hoffman, 1935). The diminished pulmonary blood flow is a convenient, if not a critical, explanation for this opinion. Refutation of this erroneous notion will be found in the report of Sloan and associates (1954).

Paradoxical embolism may occur if a right-to-left shunt exists. The source of emboli may be vegetations, either infected or bland, from the right side of the heart, or thrombi from peripheral veins. In a case seen by the author, paradoxical embolism to the superior mesenteric artery resulted in infarction of the intestine. The embolus was believed to have arisen in a peripheral venous thrombus.

SURGICAL CORRECTION

The principles involved in treatment of anatomic tetralogy of Fallot depend on the degree of pulmonary obstruction. Some patients have severe stenosis or atresia, with the problems of a large right-to-left shunt; others have mild or moderate pulmonary stenosis.

Severe obstruction to pulmonary flow may be surgically corrected by anastomosis of the aortic arch to one of the pulmonary arteries (Blalock and Taussig, 1945, Potts *et al.*, 1946). The essential effect of this operation is the production of a greater volume of pulmonary blood flow; the elimination of cyanosis is reflected in a rise in oxygen concentration of the aortic blood (Montgomery *et al.*, 1948; Potts and Gibson, 1948; Taussig, 1948; Leininger *et al.*, 1951; Taussig and Bauersfeld, 1953). While the effects of the right-to-left shunt are minimized by an increase in pulmonary blood flow, certain hazards are intrinsic in the anastomotic procedure. Balmson and Ziegler (1950) studied 99 fatalities among 500 patients in whom such an operation was performed for congenital cyanotic cardiac disease. In 15 instances in which death resulted from congestive failure or pulmonary edema, it was thought that the anastomotic stoma had been larger than ideal. Postoperative complications include cerebral infarction (Balmson and Ziegler, 1950, Berthrong

and Sabiston, 1951), cerebral abscess (Baker *et al.*, 1949), and bacterial endocarditis (Taussig, 1948) which may be located at the anastomotic site.

Operations for the relief of severe pulmonary stenosis in the anatomic tetralogy of Fallot (Sellors, 1948; Brock, 1948, 1949, 1950, 1952; Glover *et al.*, 1950, 1952; Downing *et al.*, 1951) are designed not to create an anastomotic stoma but to relieve the stenosis, either directly by resection of infundibular tissue or by creation of a pulmonary valvulotomy, or by both procedures. The primary disturbances are attacked directly without the creation of an additional abnormality. An obstacle to success with this procedure is the presence of atresia at some point in the tract leading to the pulmonary artery.

With the aid of extracorporeal circulation, a surgical procedure may be instituted to close the communication between the right ventricle and aorta and adequately to enlarge the infundibulum and pulmonary arterial tract (Lillehei *et al.*, 1955). Patients in whom the defect is closed and the obstruction to pulmonary blood flow is overcome may be returned to normal cardiac function.

Treatment of patients with *mild or moderate pulmonary stenosis* is concerned with elimination of the left-to-right shunt. This degree of pulmonary stenosis exerts a protective function in the presence of a large ventricular septal defect. Therefore, one should not attempt to relieve the pulmonary stenosis if the ventricular septal defect is not to be closed. Surgical therapy consists of closure of the ventricular septal defect and sufficient resection of the obstructive lesion to eliminate any stenosis between the right ventricle and the pulmonary arteries.

DEVELOPMENTAL BASIS

The developmental basis for the anatomic

tetralogy of Fallot resides in *maldevelopment of the truncus arteriosus*. References to Chapter II will show that the primitive truncus arteriosus is divided by a spiral septum which converts the single vessel into the pulmonary trunk and the ascending aorta, each resulting vessel being of about the same diameter. In the anatomic tetralogy of Fallot, it appears that the eccentric position of the truncoconal septum results in two vessels of unequal size. Since the partitioning of the outflow portion of the embryonic ventricle is accomplished in part by the lower portion of the truncoconal septum, one will understand that similar malposition of the septum will result in infundibular stenosis.

The explanation for intraventricular communication follows. The membranous septum is said to be absent in this condition. In examination of such hearts it is, however, possible frequently to find a tag of tissue which seems to represent rudimentary membranous ventricular septal tissue. In all probability, this is the component of the membranous ventricular septum that is contributed by the anterior atrioventricular endocardial cushion. In malposition of the truncoconal septum, its lower portion is not in line with the plane of the muscular septum and, therefore, the truncoconal septum and the muscular septum cannot unite. The ventricular septal defect then may be regarded, in part, as a deficiency of the membranous portion of the septum and, in part, as a space between the uppermost portion of the muscular septum and the origin of the aorta.

COMMON (SINGLE) VENTRICLE

A single ventricle may be further characterized by whether it is associated with a single or a divided atrium. When two atria and one ventricle are present, the condition is called *cor trilobulare biatriatum*. When a single atrium and a single ventricle are present, the condition is called *cor bilobulare*.

Cor Trilobulare Biatriatum

In this condition the two atria are normally

developed and their venous connections are normal. The atrioventricular valves are normal so that the common ventricle receives blood directly from each atrium, but the configuration of the ventricles and the relationship of the great arteries differ from normal. Most of these hearts have one of two patterns. More commonly, the great vessels are transposed and the aorta lies anterior and parallel to the pulmonary trunk. The pulmonary trunk

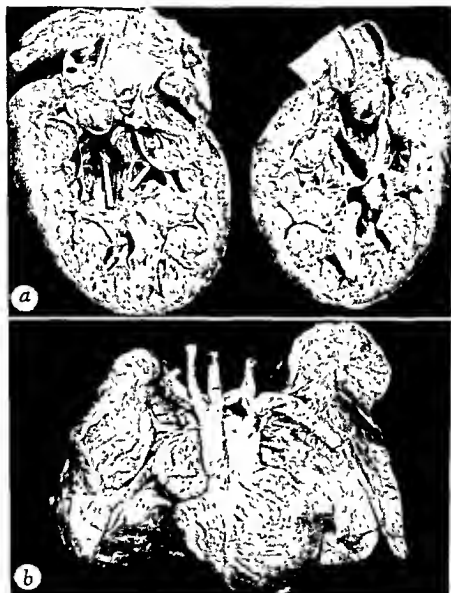


Figure VI-55. Cor triloculare biatriatum without pulmonary stenosis and with transposition of the great vessels. From a female infant 5 months old. *a*. An incision from a right anterior to a left posterior position has divided the single ventricle and the great arteries. The two halves have been swung open, as though on a hinge. In the photograph to the left, the probes are in the tricuspid and mitral orifices. The aorta lies anterior to the pulmonary trunk, and is narrower than the latter. A muscular band, crista supraventricularis, divides the outflow tract of the ventricle into a wide subpulmonary and a narrow subaortic channel. *b*. Heart, lungs, and great vessels. The great vessels are transposed, the relatively narrow ascending aorta lying to the right and in front of the wide pulmonary trunk. Also, that part of the aortic arch between the origins of the left common carotid and the subclavian arteries is narrow. Coarctation of the aorta is present between the left subclavian artery and the ligament arteriosum.

is wide and no obstruction exists between it and the common ventricle. In the second type of cor triloculare biatriatum, the pulmonary blood flow is obstructed. The two great arteries are related to each other, essentially as in the anatomic tetralogy of Fallot, the aorta taking origin to the right of the pulmonary trunk.

In most cases without pulmonary stenosis, the outflow portion of the ventricle is divided into a wide, posterior subpulmonary part and a narrower, anterior subaortic compartment. The muscle in the outflow portion of the common ventricle is so oriented that it may cause considerable narrowing at the site of communication of the subaortic chamber with the rest of the common ventricle (Figures VI-55 and VI-56). The general arrangement in cor triloculare biatriatum without pulmonary stenosis is essentially identical with that in corrected transposition of the great vessels, except that in cor triloculare biatriatum, by definition, the ventricular septum is absent.

In cor triloculare biatriatum with pulmonary stenosis, the outflow portion of the heart is divided into a right posterior subaortic portion which is not obstructed and a left anterior subpulmonary portion which has an intramural tract (Figure VI-57). This often is the site of obstruction between the common ventricle and the pulmonary arteries, although in some cases (Campbell *et al.*, 1953) the pulmonary valve is stenotic.

In less common varieties of cor triloculare biatriatum, the relationship between the aorta and the pulmonary trunk is normal (Drey *et al.*, 1938).

The incidence of cor triloculare biatriatum is relatively low. Among 357 consecutive cases in the pathologic collection of the Mayo Clinic, Fontana (1958) found 11. On review of 81 cases of cor triloculare biatriatum, most of which were taken from the literature, Campbell and associates (1953) found no obstruction to pulmonary flow in 42; pulmonary atresia in 15; and valvular and, or, infundibular obstruction in 24. Among 20 instances of cor triloculare biatriatum studied by the author, 16 did not have pulmonary stenosis, 3 had infundibular pulmonary stenosis, and one did not have an abnormal relationship between the great arteries or any pulmonary stenosis.

The sex distribution in cor triloculare biatriatum is about 2:1 in favor of the male.

The functional features depend on the relative size of the aortic and pulmonary channels. Hearts without pulmonary stenosis are essentially similar functionally to those with ventricular septal defect without pulmonary stenosis. Pulmonary hypertension is associated. In the early stages there is an excess pulmonary flow (Megevand *et al.*, 1953; Ferencz *et al.*, 1954). Later, with development of the occlusive vascular changes (Edwards and Chamberlin, 1951; Heath, 1957), a significant right-to-left shunt may appear.

The degree of saturation of the blood in the aorta and in the pulmonary trunk may be identical (van Buchem *et al.*, 1954). Usually, however, the findings on catheterization in cor triloculare biatriatum without pulmonary stenosis are similar to those in a large ventricular septal defect (Brow *et al.*, 1958). The oxygen saturation is lower in the pulmonary arteries than in the aorta. This indicates that although the blood from the 2 atria enters the common chamber, the

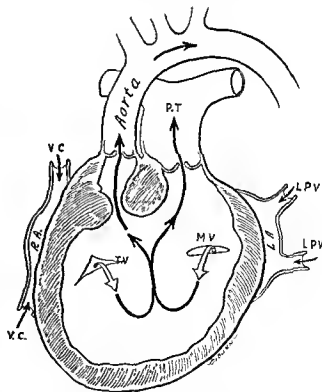


Figure VI-56. Cor triloculare biatriatum without pulmonary stenosis. Both atrioventricular orifices lead into the common ventricle. Subaortic stenosis is created through orientation of the crista supraventricularis. Blood coming from the mitral orifice tends to be directed toward the aorta and blood entering through the tricuspid orifice tends to be directed toward the pulmonary trunk. (From Edwards and Chamberlin, 1951. Reproduced with permission.)



Figure VI-57 Cor triloculare biatriatum with subpulmonary stenosis. From a 4-year-old girl. The common ventricle, aorta (A.) and pulmonary trunk (P.) are shown. There is no obstruction beneath the aortic valve. An intramural, narrow muscular tract leads to the pulmonary valve. The pulmonary valve is bicuspid.

two streams maintain their identity so that the left atrial stream tends to flow to the aorta and the right atrial stream to the pulmonary trunk.

Patients with pulmonary stenosis have a low pulmonary arterial pressure and a significant right-to-left shunt. These conditions are indistinguishable clinically from those in patients with anatomic tetralogy of Fallot and severe pulmonary stenosis or atresia (Campbell *et al.*, 1953).

Conditions associated with cor triloculare biatriatum include patent ductus arteriosus, obstruction of the aorta, mitral stenosis and isolated dextrocardia. Rawson and Doerner (1953) reported that, in a 48-year-old man with cor triloculare biatriatum but no pulmonary stenosis, the right atrium received the pulmonary veins while the left atrium received the systemic veins.

Since the functional derangements of cor triloculare biatriatum depend on the relative size of the aortic to the pulmonary tract, the conditions to be entertained in the differential diagnosis are similar to those considered in the differential diagnosis of ventricular septal defect without

pulmonary stenosis and ventricular septal defect with pulmonary stenosis (anatomic tetralogy of Fallot). The clinical differentiation of cor triloculare biatriatum from ventricular septal defect is difficult. The angiocardiogram is not specific and cardiac catheterization may not be helpful. An exception was the case reported by Deuchar (1952) in which the cardiac catheter supposedly entered the right ventricle and then passed through the mitral valve into the left atrium and pulmonary veins. Under these circumstances the suspicion of a single ventricle may be entertained. Electrocardiographically, the signs may not be different from those of patients having ventricular septal defect. The unusual finding of essentially similar QRS complexes in all precordial leads might suggest the presence of a single ventricle (Freireich and Nicolson, 1952). Roentgenographic examination is not a distinguishing feature. Patients having cor triloculare biatriatum and no pulmonary stenosis yield signs which are similar to those of patients having ventricular septal defect without pulmonary stenosis (Figure VI-58a and b), whereas patients having cor triloculare biatriatum with pulmonary stenosis usually present roentgenographic signs which are indistinguishable from those in the tetralogy of Fallot with severe pulmonary obstruction (Figure VI-58c and d).

The complications of cor triloculare biatriatum likewise follow the pattern set by ventricular septal defect. When no pulmonary obstruction exists, death associated with excessive pulmonary flow is common during early infancy. Later the complications of pulmonary vascular obstruction and the appearance of a significant right-to-left shunt are important features. Patients with pulmonary obstruction suffer from the right-to-left shunt, including anoxic episodes, and may develop a cerebral abscess.

The prognosis in cor triloculare biatriatum varies considerably. In their review of 85 cases, Campbell and associates (1953) found that more than half of the patients died within the first year of life, but 18 reached the age of 20 years, the oldest being 56 years. Prognosis is poorest for patients who do not have pulmonary obstruction and for those with pulmonary obstruction resulting from pulmonary atresia. In general, patients with pulmonary stenosis survive longest. References to unusual longevity are to be found in the reviews of Rogers and Edwards (1951), Barry and Isaac (1953), Campbell and associates (1953), and Heath (1957).

Cor Biloculare

Cor biloculare represents the most primitive type of heart encountered, in that it has a single atrium and a single ventricle. Malformations of the great vessels frequently are associated. The single atrium usually shows a strand of abortive septal tissue which runs from the anterior to the posterior wall above

the common atrial valve (Figure VI-59a). As a rule, there are 2 atrial appendages, a persistent left superior vena cava and a right superior vena cava. The left superior vena cava terminates at the left portion of the superior aspect of the common atrium. Under these circumstances, the coronary sinus is absent (Figure VI-59a). Below the common atrioventricular valve is a single ventricle. The

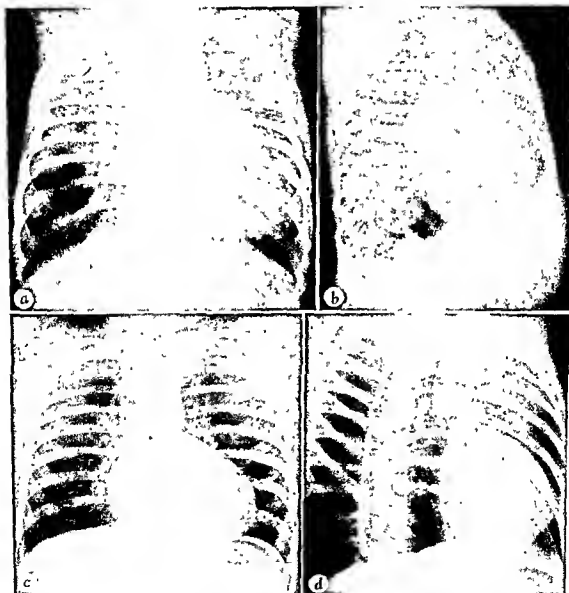


Figure VI-58. Roentgenograms of thorax in two cases of cor triloculare biatriatum, without pulmonary stenosis in one case and with pulmonary stenosis in the other. *a* and *b*. From a 3-month-old male infant without pulmonary stenosis. *a*. Postero-anterior view showing evidence of increased pulmonary vascularity. *b*. Lateral view, showing sub-sternal prominence resulting from the anterior position of the ascending aorta. *c* and *d*. From a 4-year-old girl with subpulmonary stenosis whose specimen is illustrated in Figure VI-57. *c*. Anteroposterior view, showing concavity in anticipated location of the pulmonary trunk and evidence of decreased pulmonary flow in the pulmonary fields. *d*. Right anterior oblique view, showing concavity at the region of the pulmonary trunk, and decreased vascularity of the pulmonary fields resulting from diminished pulmonary blood flow.



Figure VI-59 Cor biloculare in an 11-year-old girl who also had agenesis of the spleen. *a* Right side of heart. In front of the orifice of the inferior vena cava (I.V.C.) is a strand of abortive septal tissue running between the posterior and anterior walls of the common atrium. There is no coronary sinus, inasmuch as the left superior vena cava had joined the left side of the common atrium. *b* The ventricle and aorta. Behind the unopened aorta, the probe lies in a stenotic intramuscular tract which connects with a wide pulmonary trunk.

arrangement of the great arterial system varies. Usually, the aorta lies anterior and parallel to the pulmonary trunk, while the pulmonary trunk is stenotic or atretic and, in some instances, may not even be identifiable. When pulmonary obstruction is severe, a ductus arteriosus is the usual route by which the blood is carried into the pulmonary arterial system. Frequently a stenotic subpulmonary infundibular tract runs through the muscle of the common ventricle. The ventricular orifice of this tract lies in the posterior wall of the common ventricle (Figure VI-59b).

Severe pulmonary obstruction may be associated with the presence of transposed great vessels (Kugel, 1932; Rossman, 1942; Miskall and Fraser, 1946). A persistent truncus arteriosus may be encountered occasionally (Giustra and Tosti, 1939; Coltman and Stern, 1939; Michelson, 1943). Rarely the aorta and pulmonary trunk are properly interrelated and neither is obstructed (Derow, 1934). A right aortic arch is commonly associated with cor biloculare. Anomalies of the venous system, in addition to persistence of left superior vena cava, are common. These include total anomalous venous connection and malforma-

tions of the inferior vena cava. In a case described by Campbell and associates (1952), the hepatic veins joined the common atrium; the rest of the blood from regions below the diaphragm was carried by way of an enlarged azygos vein to the superior vena cava.

Many patients with cor biloculare have *agenesis of the spleen* and associated visceral malformations, as situs inversus of the stomach and incomplete rotation of the mesentery (see reviews of Ivemark, 1953; Putschar and Manion, 1956; and Gilbert *et al.*, 1958).

Incidence. Fontana (1958) encountered cor biloculare only 6 times among 357 examples of malformations of the heart and great vessels from patients of all ages. The *sex distribution* is about equal in our experience.

The *functional derangement* depends principally on the relative size of the aortic and pulmonary tracts. The greater the degree of pulmonary obstruction, the greater will be the right-to-left shunt. In severe pulmonary obstruction, the ultimate arterial oxygen saturation in the aorta will depend on the volume of collateral blood flow to the lungs; the greater this flow, the higher the desaturation. The appearance of the patients, therefore, may vary widely. Cyanosis is commonly, but not invariably, present. The problems are the same as those inherent in interpretation of

special tests in cor triloculare batriatum. The presence of a single atrioventricular orifice, frequently coupled with venous malformations, makes the chance greater that a ventricular sample of blood will be a true mixture. Under these circumstances the level of oxygen saturation of the ventricular and aortic blood may be identical. Such a finding may suggest the presence of a two-chambered heart but does not exclude complete transposition of the great vessels.

The conditions to be entertained in the differential diagnosis depend on the level of oxygen saturation of the arterial blood. If the desaturation of arterial blood is considerable, among other conditions, one must exclude complete transposition of the great vessels, anatomic tetralogy of Fallot with severe pulmonary stenosis, and total anomalous pulmonary venous connection. If the oxygen level in the systemic arterial blood is not sufficiently low to cause cyanosis, the conditions to be ruled out are ventricular septal defect without pulmonary stenosis and other functionally related lesions. The finding, in smears of the peripheral blood, of Heinz-Elhrich bodies or Howell-Jolly bodies and other hematologic manifestations of asplenia (Polhemus and Schafer, 1955; Willi

and Gasser, 1955; Lyons *et al.*, 1957) often suggest the presence of cor biloculare because of the common, but not invariable, association of this cardiac malformation with congenital asplenia.

The prognosis in cor biloculare is generally poor, most patients surviving less than 1 year. Death usually results from the effects of severe hypoxia. The author has observed 2 unusual cases; in 1, the patient reached the age of 10 years and had bacterial endocarditis of the common atrioventricular valve; in the other, the patient lived to the age of 11 and had chronic glomerulonephritis. Taussig's patient (1947) lived 25 years.

At present no operative procedure is curative. If pulmonary stenosis is severe, an aortopulmonary anastomosis should increase the pulmonary blood flow and consequently the oxygen saturation in the aorta.

The malformation seems to result from an arrest in development at an early stage. Frequently associated is pulmonary stenosis or atresia which apparently results from eccentric partitioning of the truncocoanal channel.

ANEURYSM OF MEMBRANOUS SEPTUM

Aneurysms of the ventricular septum involve the pars membranacea. While usually of no clinical significance, they may cause a disturbance in atrioventricular conduction (Clark and White, 1952; Rogers *et al.*, 1952). They are represented by an outpouching of the membranous septum toward the right. The mouth of the aneurysm lies inferior to the aortic orifice (Figure VI-60). On the right side, the base of the aneurysm bulges either into the right ventricle, beneath the septal leaflet of the tricuspid valve, or into the base of the right atrium just above the septal leaflet of the tricuspid valve (Cannell, 1930).

The lesion is rare. Up to 1938, about 70 cases had been reported (Lev and Saphir, 1938). (See also reports and reviews by Leckert and Sternberg, 1950; Vaněček, 1950; and Rogers *et al.*, 1952.)

Although a variety of theories of etiology have been presented, Lev and Saphir regarded most of the aneurysms as truly congenital. They recognized that theoretically an inflammatory process may lead to an aneurysm in this region but

pointed out that existing aneurysms may become infected and cause difficulty in determining the course of events.

Mall (1912) reported an aneurysm of the membranous portion and stated that the malformation may be traced to an embryonic arrest of development. In this condition, the muscular portion of the septum does not move to the right sufficiently but remains with the vestibule of the aorta, as is normally the case in the ox and pig. Consequently, the membranous portion assumes a horizontal rather than a vertical position. It is thereby weakened and predisposed to formation of an aneurysm. Mall concluded that aneurysms of the ventricular septum were not the result of endocarditis but of anomalous position of the aorta to the right, and of displacement of the muscular septum to the left, thus causing the membranous portion of the septum to assume a horizontal position.

It is, however, unsettled whether displacement of the muscular portion of the septum to the left is the basic cause of aneurysms of the membranous portion. The case of Rao (1936) suggests an association between the aneurysm and a prominence of the muscular portion of the septum



Figure VI-60 Aneurysm of membranous portion of ventricular septum in a 70-year-old man. (From Rogers *et al.*, 1952. Reproduced with permission of C. V. Mosby Company.) *a*, Right side of heart. The aneurysm is closely related to the septal leaflet of the tricuspid valve. *b*, Left ventricle. The aneurysm lies principally beneath the right cusp of the aortic valve.

toward the left. Her patient was a man 63 years of age who, in addition to an aneurysm of the membranous septum, had subaortic stenosis. In a subsequent section (see page 370), the opinion is expressed that subaortic stenosis is probably related to an unusual prominence toward the left of the muscular portion of the ventricular septum. If this is correct, then the interpretation of Mall seems to be supported by the case of Rae.

In the section on defects of the endocardium, it was pointed out that a persistent common atrio-ventricular canal is frequently associated with mongolian idiocy. Thus cardiac malformation is readily traced to faulty development of the atrio-ventricular endocardial cushions.

The 2 patients of Lev and Saphir (1938), with aneurysm of the ventricular septum, were mongolian idiots. These cases suggest that aneurysm

of the ventricular septum is associated with some basic abnormality in development of the atrio-ventricular endocardial cushions. It will be recalled that these cushions play a role in the development of the pars membranacea. Case 1 of Rogers and associates (1952) was similar to the cases of Lev and Saphir in that an aneurysm of the pars membranacea was found in the heart of a Mongolian idiot. In this case, as in that of Rae, there was also some degree of subaortic stenosis. Zadoc-Kahn and Cousin (1925) reported a case of aneurysm of the ventricular septum and complete absence of the atrial septum in a man aged 31 years. With the aid of angiocardiology, Steinberg (1957) diagnosed an aneurysm of the membranous septum in a living patient.

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Ventricular Septal Defect without Pulmonary Stenosis

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Congenital Malformations

C. Malformations Resulting from Abnormalities in Partitioning of Truncus and Conus Arteriosus

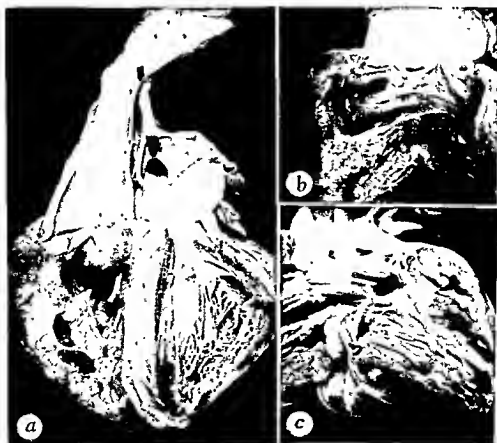
JESSE E. EDWARDS

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COMPLETE TRANSPOSITION OF THE GREAT VESSELS

TRANSPOSITION MAY BE defined as any congenital abnormality in the relationship of the great arterial vessels to each other and to the ventricles. The tetralogy of Fallot, the

Taussig-Bing complex, and persistent truncus arteriosus may be regarded as varieties of transposition. This section, however, is concerned with another well-defined condition



designated *complete transposition of the great vessels*. Some hearts in which the great vessels are related abnormally, as in complete transpositions, have a single ventricle anatomically; others have two ventricular chambers but either the mitral or the tricuspid valve is atretic and both ventricular chambers function together as though one chamber existed. It seems advisable to reserve for this class of malformations, hearts having two ventricles which are anatomically and functionally separate. By so doing, we emphasize that this condition is an entity with rather clear-cut clinical and pathologic features.

It is essential to distinguish instances of transposition in which the two ventricles function as separate ventricles from hearts having a single ventricle or two ventricles that function as a single ventricle. In the former condition (complete transposition of the great vessels), the basic and important consideration is that the blood which has passed through the lungs is unable to reach the aorta and to be carried to the greater circulation. In the second group, the abnormal position of the vessels is in itself of little functional consequence since the venous and oxygenated blood which flows through the ventricular part of the heart either is mixed blood or is directed to the proper vessels.

Pathologic Anatomy. The *aorta* arises exclusively from the right ventricle and the *pulmonary trunk* exclusively from the left ventricle (Figures VI-61 and VI-62). The aorta lies ventral to and on a plane slightly to the right of the pulmonary trunk. The two vessels run parallel to each other, failing to cross each other as they normally should. The *ventricular system* is present but, in about a third of the cases (Hanlon and Blalock, 1948), has a defect in its outflow tract. Lev and Saphir

(1937) have indicated that when the ventricular septum is closed, it is formed entirely of muscular tissue. Usually in complete transposition, the *right atrium* communicates in a normal manner with the venae cavae and the coronary sinus, and also with the right ventricle through the tricuspid orifice. The left atrium receives the pulmonary veins and empties its blood through the mitral valve into the left ventricle. The atrioventricular valves are normally developed, the pulmonary valve lies posteriorly, and thus the anterior leaflet of the mitral valve joins the pulmonary valve in a manner comparable to the connections between the mitral and aortic valves of normal hearts (Figure VI-63).

The association of pulmonary stenosis and complete transposition of the great vessels (Lewis, 1948) is mentioned in more than a third of the

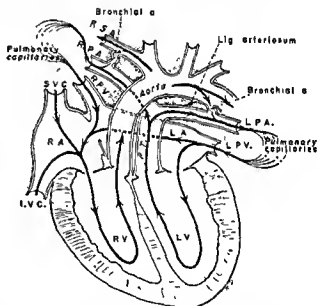


Figure VI-62. Complete transposition of the great vessels. Diagrammatic representation of Cockle's case (1863) in which the two sides of the circulation communicated by means of dilated bronchial arteries and a patent foramen ovale.

Figure VI-61. Complete transposition of the great vessels.

a. The aorta arises from the right ventricle and the pulmonary trunk from the left ventricle. The ductus arteriosus is patent. From a male infant 3 months old (Reproduced by permission of Postgraduate Medicine.)

b. The aorta arises from the right ventricle. The ventricular septum is closed and the coronary arteries arise from the aorta. From a male infant 1 month old.

c. The aorta arises from the right ventricle and ventricular septal defect (containing a probe) is present. Probes have also been inserted into the ostia of the coronary arteries, which arise from the aorta. From a female infant 7 months old.

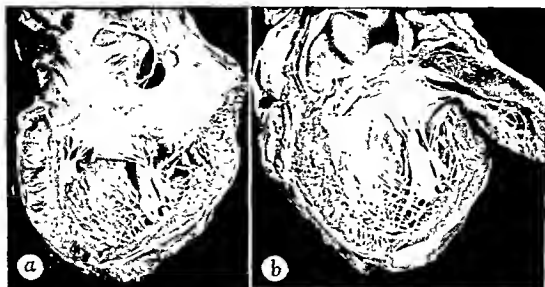


Figure VI-63. Complete transposition of great vessels with atrial and ventricular septal defects

a. Left atrium and left ventricle. Atrial septal defect is present in region of fossa and left atrioventricular valve has the configuration of a normal mitral valve.

b. Left ventricle and pulmonary trunk. A ventricular septal defect lies inferior to the pulmonary trunk. The relationship of the mitral and pulmonary valves in this specimen with complete transposition of great vessels is like that of the mitral and aortic valves in normal hearts.

cases reported (Becker and Brill, 1948). In our experience, however, pulmonary stenosis is not commonly associated. At times a bicuspid pulmonary valve may be present (Hemsath *et al.*, 1936, Case 4). The coronary arteries arise from the aorta. Keith and associates (1953) studied the relations of the coronary arteries to the aortic cusps in 37 specimens of complete transposition. The positions of the coronary arterial ostia were given according to the aortic cusps behind which the arteries arose. The aortic cusps were designated as "posterior, right anterior and left anterior." In 34 of their 37 cases, the right coronary artery arose behind the posterior cusp, in the other 3, from the sinus of the right anterior cusp. The left coronary artery arose from the sinus of the left anterior cusp in 34 cases; in the other 3, from the sinus of the posterior aortic cusp.

Usually the auricular appendages lie in normal position. In a case reported by Muskall and Fraser (1948) and in a case observed by the author, the right auricular appendage lay to the left of the great arterial vessels and just to the right of the left auricular appendage (Figure VI-64). The term *juxtaposition of the atrial appendages* was suggested for the condition by Dixon (1954). It may occur in other varieties of transposition of the great vessels. Juxtaposition of the auricular

appendages is of no functional significance but, during cardiac catheterization or on angiocardiology, the position of the right auricular appendage on the left side of the great vessels may be confusing.

The severe cyanosis, which is characteristic of transposition of the great vessels, results from origin of the aorta from the right ventricle (carrying venous blood) while the pulmonary trunk arises from the left ventricle (carrying oxygenated blood). In the basic malformation no arrangement is provided for orderly passage of venous blood through the lungs and then to the systemic arterial circulation. If life is maintained after the umbilical cord is interrupted, it means that some communication, however small, must exist between the lesser and greater circulations or between the two sides of the heart.

The three most common means of communication are patent foramen ovale, ventricular septal defect, and patent ductus arteriosus. In a given case, one, two, or all three of these may be present. Additional sources of communication between the two circulations may exist and should be looked for by the

pathologist at necropsy in all hearts with this condition. Anomalous connection of one or several pulmonary veins with the right atrium or one of its tributaries would permit a substantial amount of arterialized blood to reach the right side of the heart and then the aorta, for distribution to the systemic circulation.

This was the situation in the patient of Feldman and Chalmers (1933), who lived to the age of 2 months. All of the pulmonary veins entered the right atrium, and a patent foramen ovale was the avenue by which the left side of the heart received blood. In a male infant, aged 22 months, with complete transposition of the great vessels, Harris and associates (1927) reported that an anomalous vein connected the right internal jugular vein with the left atrium. In addition, the heart had an atrial septal defect represented as incomplete guarding of the foramen ovale by its valve, a ventricular septal defect and a patent ductus arteriosus. It is conceivable that the anomalous vein played a role either in bringing venous blood to the left side of the heart for oxygenation in the lungs or in carrying oxygenated blood from the left atrium to the right side of the heart and so to the aorta. A similar venous variation was noted in the fifth case of Read and Krumbhaar (1932), in which the azygos vein communicated with the left atrium.

Abbott (1937) stressed that dilated bronchial arteries may be another important channel of getting the blood from one system into the other in complete transposition of the great vessels (Figure VI-65). Cockle's (1863) patient, a boy aged 2 years and 8 months, had complete transposition of the great vessels, a patent foramen ovale, and greatly dilated mediastinal vessels leading to the lungs, which were probably bronchial arteries. The ventricular septum and the ductus arteriosus were closed (Figure VI-62). By injection techniques, Cudkovic and Armstrong (1952) demonstrated enlarged bronchial arteries in a heart with complete transposition of the great vessels.

Incidence. Complete transposition of the great vessels is relatively common among congenital cardiac malformations of infants and children.

Gibson and Clifton (1936) observed this condition 9 times in 105 specimens of congenital cardiac disease in infants and children. Terplan and Saues (1936) found at necropsy 21 cases of

congenital cardiac disease, including 1 instance of complete transposition among 336 infants 1 year of age or less. Among 300 children with congenital heart disease studied clinically, Astley and Parsons (1952) found 72 who were cyanotic; it was thought that 36 of these had tetralogy of Fallot and 16, complete transposition of the great vessels. In the collection of 357 specimens at the Mayo Clinic, Fontana (1958) found 24 examples of complete transposition of the great vessels.

Sex Distribution. Males predominate, the ratio being about 4 males to 1 female.

Functional Features. The primary disturbance in complete transposition of the great vessels is based on communication of the aorta with the right ventricle and of the pulmonary trunk with the left ventricle, all of the other connections being normal. As a result, unsaturated blood in the right side of the heart is primarily directed to the aorta while completely saturated blood from the left ventricle is directed to the pulmonary trunk for recirculation. It has been pointed out that, for life to be maintained, blood must communicate between the two circulations.



Figure VI-64. Juxtaposition of the auricular appendages in a case of complete transposition of the great vessels. The right auricular appendage (R.A.) lies to the left of the great vessels (A. indicates aorta; P.T., pulmonary trunk) and to the right of the left auricular appendage (L.A.).



Figure VI-65. Anterior aspect of trachea and aortic arch in an infant with complete transposition of the great vessels. The aortic arch has been deflected toward the patient's left. A large bronchial artery arises from the distal portion of the aortic arch, crosses in front of the trachea and communicates with the right lung near the right main bronchus.

Campbell and associates (1949) suggested that when the volume of blood on one side of the heart becomes significantly greater than on the other, the pressure rises on the side to which the blood is shunted, causing reversal of the shunt. Becker and Brill (1948) thought that, during ventricular systole, the blood flow was from the left to the right through a ventricular septal defect, but during diastole the flow might be in the reverse direction.

It is probable that blood flowing through large bronchial arteries passes from the aorta into the pulmonary circulation. In some instances of complete transposition of the great vessels, the distal portion of the body is less cyanotic than the proximal part, indicating that the flow is from pulmonary artery into the aorta through the ductus arteriosus. The patient of Dreyfuss (1929) had coarctation of the aorta proximal to the patent ductus arteriosus, but this additional malformation need not be present for blood to flow in the direction named.

Among patients having ventricular septal defect, pulmonary hypertension is probably always present, as it may be in patients having patent ductus arteriosus. It is not known whether the pulmonary arterial pressure is normal when the ventricular septum is intact. When the ventricular septum is present, the pulmonary vessels may show hypertensive changes like those seen in ordinary ventricular septal defect (Figure VI-66).

Clinical Features (reviewed by Taussig, 1938; Campbell and Suzman, 1951; Astley and Par-

sons, 1952; Keith *et al.*, 1953; Rushmer *et al.*, 1953). Usually cyanosis, often intense, is an early sign and is noted immediately after birth. Increased vascular markings throughout the lungs in the roentgenogram of a cyanotic patient provide strong evidence of this condition; the shadow of the great vessels may be narrow in the anteroposterior projection and wider in oblique views (Keith *et al.*). The patient often presents evidence of rapid cardiac enlargement and early congestive heart failure. Cardiac catheterization usually indicates that the oxygen saturation of the aorta is essentially similar to that in the right ventricle. In 3 cases reported by Campbell and Suzman, the oxygen saturation of blood in the systemic arteries was slightly higher than that in the right ventricle, probably as a result of a left-to-right shunt occurring through a ventricular septal defect. In instances in which both the aorta and pulmonary artery were entered, the oxygen saturation in the pulmonary artery was significantly higher than that in the aorta. The low saturation in the aorta (Campbell and Suzman's figures ranged from 50 to 75 per cent saturation) corresponds to saturation of mixed venous blood. Various techniques for studying circulation time indicate early filling of the aorta from the right ventricle. Angiocardiographic studies reveal the filling of the aorta from the right ventricle (Abramson, 1950) and may be helpful in establishing the diagnosis, but such features may also be observed in anatomic tetralogy of Fallot with severe pulmonary stenosis or atresia, and even in hearts with a single ventricle. If a precordial systolic murmur is present, it has a close but not an absolute correlation with a ventricular septal defect, according to Keith and associates (1953).

Associated Conditions. Complete transposition of the great vessels usually is not associated with other major malformations except the communications between the circulations that have already been described. These are not ordinarily regarded as separate entities, but simply as part of the condition. The occurrence of anomalous pulmonary venous connection in association with complete transposition of the great vessels has been mentioned under Pathologic Anatomy.

Prognosis. An extensive review by Kato (1930) indicates that most patients do not survive beyond infancy, although some may reach adolescence or adult life.

Hanlon and Blalock (1948) reviewed the survival time in 123 cases of transposition taken from the following sources: 85 of the 97 cases reviewed by Kato in which data were sufficient for analysis; isolated cases reported following publication of Kato's paper; and 23 cases studied at necropsy at the Johns Hopkins Hospital. The average duration of life in this series of 123 cases was 19 months. They stated that, exclusive of 6 patients who survived 10 years or longer, the average age at death (of 117 patients) was 5½ months. They emphasized the importance of communications between the two sides of the heart, namely, atrial septal defect, ventricular septal

defect, and also patent ductus arteriosus. They emphasized particularly the beneficial effects of a ventricular septal defect and of combinations of intercommunication. Several of the cases reviewed by Kato which favorably influence the average age of survival should not be included under the designation of complete transposition of the great vessels. On the other hand, Dornig's (1890) patient, a boy 8½ years old, represents a *bona fide* example of complete transposition of the great vessels with unusually long survival. The patient of Alexander and White (1947) lived 17 years and that of Pung and associates (1955), 18 years.

TAUSSIG-BING COMPLEX

In 1949 Taussig and Bing described the complex of malformations in which the aorta arose entirely from the right ventricle, and the pulmonary trunk arose from both ventricles above a ventricular septal defect. There was no pulmonary stenosis (Figures VI-67 and VI-68).

Earlier, Shapiro (1930) and Brown (1939) had described a similar arrangement. Brown indicated that this condition was a variant of complete transposition of the great vessels, a view with which the author agrees. In spite of the historical sequence, this complex of malformations is now known as the *Taussig-Bing complex*. This variant of complete transposition of the great vessels is uncommon (review by Chiechi, 1957). While pulmonary stenosis was absent in the cases initially described, the author has observed a case with pulmonary stenosis. This might be called "Taussig-Bing complex with pulmonary stenosis."

In the classic example of the condition without pulmonary stenosis, the functional arrangements depend on presence of a large ventricular defect and on origin of the aorta directly from the right ventricle. Considerable pulmonary recirculation occurs, and the pulmonary arterial oxygen saturation is at a higher level than that of the aorta. The desaturation of the blood in the aorta is responsible for cyanosis. The paradox of cyanosis in the presence of increased pulmonary flow should suggest complete transposition of the great vessels or this variant of it.

Angiocardiographic evidence of early filling of the aorta and later filling of the left side of the heart and pulmonary trunk leads one to suspect the condition (Van Buchem *et al.*, 1950, Martin

and Lewis, 1952; Azevedo *et al.*, 1956). Pulmonary hypertension is present in cases without pulmonary stenosis (Taussig and Bing, 1949, Metianu *et al.*, 1953; Dubourg *et al.*, 1954).

Not infrequently the Taussig-Bing complex is



Figure VI-66. A large muscular artery of the lung of a 5-year-old child who had complete transposition of the great vessels and large ventricular septal defect. The artery shows medial hypertrophy and considerable intimal fibrous thickening, causing corresponding narrowing of the lumen. Elastic tissue stain. X 115.

associated with anomalies of the aortic arch system (Maxwell and Crumpton, 1954). These include patent ductus arteriosus (Lev and Volk, 1950), anomalous origin of the right subclavian artery, and coarctation of the aorta (Mossberger, 1949). In an unusual case reported by Alcott and associates (1956), an anomalous right subclavian artery arose proximal to the site of aortic coarctation (Figure VI-67).

BIVENTRICULAR ORIGIN OF PULMONARY TRUNK WITH SUBAORTIC STENOSIS

In 1955 Becu and associates described a complex of malformations which was characterized by the biventricular origin of the pulmonary trunk, subaortic stenosis and frequently associated malformations of the aortic arch system (Figures VI-69 and VI-70). The chief characteristic of this malformation is that the ventricular septal defect, when viewed from the right side, is located above the papillary muscle of the conus and in close relation to the pulmonary valve. A portion of the upper edge of the defect is formed by the pulmonary valvular tissue at the commissure between the left and right pulmonary cusps. The outflow tract of the

The prognosis in the Taussig-Bing complex is generally better than in the classic varieties of complete transposition of the great vessels where each of the great arteries arises exclusively from the "wrong" ventricle. The large ventricular septal defect in this condition allows for more mixing of blood than in the pure form of complete transposition of the great vessels.

left ventricle is divided by a muscular ridge which runs from the anterior leaflet of the mitral valve to the anterior wall of the left ventricle (Figure VI-69b). This muscular ridge divides the outflow tract into a narrow subaortic tract beyond which the aorta arises, and a tract which leads to the ventricular septal defect. The various associated malformations of the aortic arch includes patent ductus arteriosus with coarctation of the aorta and interruption of the aortic arch with bilateral ductus arteriosus. All of the 5 patients whose malformations were reported by these authors died in infancy.

ORIGIN OF BOTH GREAT ARTERIES FROM THE RIGHT OR LEFT VENTRICLE

Uncommonly both the aorta and pulmonary trunk arise from one ventricle, more often the right ventricle. Under these circumstances, a ventricular septal defect is present. Witham (1957) reviewed the literature on "double outlet right ventricle" and included in this category cases of persistent truncus arteriosus arising from the right ventricle as well as those in which the two great vessels were developed but communicated only with the right ventricle. In this chapter, persistent truncus arteriosus arising from the right ventricle is discussed in the section dealing with Persistent Truncus Arteriosus and is kept separate from cases in which both great vessels are formed and arise from the right ventricle. Isolated cases of this condition were reviewed by Ash and associates (1939).

When both great arteries arise from the right ventricle, the two great vessels usually bear a relationship to each other which is essentially like that in the anatomic tetralogy of Fallot with the specimen viewed from the exterior. A ventricular septal defect is present, and the aorta and pulmonary trunk arise more or less side by side (Figure VI-71). In some circumstances the tract leading to the pulmonary trunk is not stenotic, and in others there may be infundibular stenosis. In the first edition of this chapter, the latter cases were classified as variants of the tetralogy of Fallot and cases without pulmonary stenosis were called "Eisenmenger complex."

Uncommonly the condition is intermediate between obvious origin of both great vessels from the right ventricle and anatomic tetralogy of Fal-

lot. In the last condition, the aorta clearly arises from both ventricles. In the intermediate group the aorta arises only in small part from the left ventricle. Some such cases have a subpulmonary, right ventricular, infundibular tract, while others have no such tract or any other gross obstruction to pulmonary blood flow.

In an occasional instance in which the two great vessels arise from the right ventricle, the position of the aorta with respect to the pulmonary trunk is abnormal and resembles that in complete transposition of the great vessels. Usu-

ally pulmonary or infundibular stenosis or both are present. In one such case, the author observed the additional features of persistent common atrioventricular canal.

When both of these arteries arise from the right ventricle, the *functional disturbances* depend on the presence or absence of pulmonary stenosis. If stenosis is present, the function is like that in the anatomic tetralogy of Fallot with comparable degrees of pulmonary stenosis. If pulmonary obstruction is absent, the function is essentially like that in hearts with ordinary large ventricular septal defect.

Rarely both great arteries arise from the left ventricle. When it does occur, there is a ventricular septal defect, and the great vessels are transposed, the aorta lying ventral to the pulmonary trunk. In the author's experience, the pulmonary pathway is always markedly obstructed or even atretic. Behind the origin of the transposed aorta is a stenotic or atretic muscular tract which leads from the left ventricle to the pulmonary trunk. Hypoplasia of the right ventricle may be associated.



Figure VI-67. Taussig-Bing complex. Interior of right ventricle and great vessels is shown. The pulmonary trunk (P.) arises above a ventricular septal defect (V.S.D.). In this case malformations of the aortic arch system included coarctation of the aorta (Coarc.) opposite the aortic entrance of the closing ductus arteriosus (D.A.). Beyond the origin of the left subclavian artery (L.S.A.) and proximal to the site of the coarctation is the origin of an anomalous right subclavian artery (R.S.A.). The aorta (A.) arises exclusively from the anterior portion of the right ventricle. (From Alcott and associates, 1956. Reproduced with permission of the authors and *Pediatrics*.)

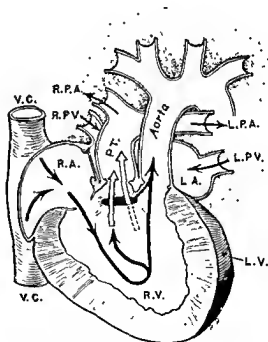


Figure VI-68. The intracardiac circulation in the Taussig-Bing complex (modified from Taussig and Bing, 1919).

CORRECTED TRANSPOSITION OF THE GREAT VESSELS

Corrected transposition of the great vessels is uncommon.

In 357 specimens of malformations of the heart

and great vessels from patients of all ages at the Mayo Clinic, Fontana (1958) found 5 instances. Cardell (1956) found only 24 cases reported in the literature.



Figure VI-69 Biventricular origin of pulmonary trunk with subaortic stenosis. (From Becu and associates, 1955. Reproduced with permission of the authors and C V Mosby Co.)

a. Interior of right ventricle and pulmonary trunk. The pulmonary valve (P.V.) is wider than normal and overrides the ventricular septal defect (V.S.D.). The latter is located above the papillary muscle of the conus (P.M.C.) and below the pulmonary valve, with a portion of the crista supraventricularis (C.S.). On the anterior wall of the outflow tract of the right ventricle is an area of endocardial thickening which is interpreted as a jet lesion resulting from a left-to-right shunt through the defect (T.V. indicates tricuspid valve).

b. Interior of left ventricle (L.V.) and aorta. The posterior papillary muscle (P.P.M.) and the anterior mitral leaflet (A.M.) are normal. Across the outflow tract of the left ventricle is a muscular ridge that divides this tract into two portions, a posterior subaortic one and an anterior one. The latter tract leads to the ventricular septal defect (V.S.D.) and beyond into the pulmonary trunk (P.T.). The aorta is narrow compared to the size of the pulmonary trunk.

The *pathologic anatomy* is specific, making the pathologic diagnosis simple (Walmsley, 1931). The principal external feature is the abnormal relationship of the aorta and pulmonary trunk which resembles that in the serious malformation, complete transposition of the great vessels. The aorta lies ventral to the pulmonary trunk and the two vessels run parallel, instead of crossing each other as they normally do. Despite the abnormal arrangement of the great vessels, the aorta and the pulmonary trunk connect with appropriate ventricles so that the route of blood flow through the heart is normal. The internal structure of the heart is also abnormal (Figure VI-72). The right ventricular wall is

smooth, resembling the wall of the left ventricle of normal hearts. The right ventricle lies dorsally. The left ventricle, which lies ventrally, is trabeculated and has muscular landmarks like those of the right ventricle of the normal heart. The respective atrioventricular valves also have features that bear resemblance, in mirrored image, to the normal contralateral valves. Thus, in corrected transposition of the great vessels, the right atrioventricular valve has two leaflets resembling, in their structure and chordal arrangements, those of the mitral valve. Here the anterior leaflet forms the wall of both the inflow and the outflow tracts of the ventricle, as does the anterior leaflet of the mitral valve in nor-

mal hearts. Moreover, the continuity of the anterior leaflet of the mitral valve with the cusps of the aortic valve seen in the normal heart is comparable to the continuity of the anterior leaflets of the right atrioventricular valve with the pulmonary valve of the heart having corrected transposition of the great vessels. In the latter condition, the left atrioventricular valve has the structure, but in the form of a mirrored image, of the tricuspid valve of the normally formed heart.

Care should be taken in the *terminology* of the atrioventricular valves in this malformation. While it is best to refer to these valves as the "left and right atrioventricular valves," for the sake of brevity, in this section we may call the left valve the "mitral" and the right the "tricuspid" valve, the quotation marks signifying free use of the terms.

Since part of the mirrored arrangement concerns the origin of the ventricles and great arteries, the pulmonary valve lies at a lower body level than the aortic, in contrast to the situation in the normal heart. In patients with this type of heart, usually the other viscera are normally disposed, but occasionally *situs inversus* may be present.

When corrected transposition is not associated with other conditions, there is no basis for cardiac dysfunction. Commonly, however, this condition is associated with other malformations, particularly ventricular septal defect.

The possible association of insufficiency of the "mitral" valve, however, has been emphasized relatively little. Helmholz and associates (1956) found that in 5 of 6 specimens with corrected transposition of the great vessels, malformations of the left atrioventricular valve either caused or could have caused incompetence of this valve. Three of the 5 specimens also had a ventricular septal defect, and a fourth specimen, a patent ductus arteriosus. Of 3 cases acquired at the Mayo Clinic since the report by Helmholz and associates, 1 showed subpulmonary stenosis and the lesion was essentially a mirrored image of the lesion of subaortic stenosis of normally disposed hearts, isolated dextrocardia also was present. The second heart had a ventricular and an atrial septal defect and the third, "mitral" insufficiency without septal defects. In a review of 17 cases of corrected transposition of the great vessels, Anderson and associates (1957) found ventricular septal defects in 6, a ventricular septal defect and an atrial septal defect in 1, and a ven-

tricular septal defect and "mitral" stenosis in 1. Three hearts had pulmonary stenosis; 1, pulmonary stenosis and ventricular septal defect, and 2, patent ductus arteriosus.

When ventricular septal defect occurs in association with corrected transposition, the defect is located in the usual position, but because of the mirrored arrangements within the heart, the defect has a different relationship to the pulmonary and aortic valves from that in the normally disposed heart. Thus, unlike the normal heart in which the ventricular septal defect is aligned closely to the aortic valve and is distant from the pulmonary valve, in corrected transposition the defect lies at some distance from the aortic valve and is adjacent to the pulmonary valve. The lesions which cause incompetence of the left atrioventricular valve take two forms. In one there is peculiar anomalous insertion of chordae which bind the valve leaflets in such a way as to prevent their complete apposition during ventricular systole. In other cases (Edwards, 1954; Becu *et al.*, 1955), the left atrioventricular valves show anomalies which are essentially mirrored images of the Ebstein malformation of the tricuspid valve of normally disposed hearts. In such cases there

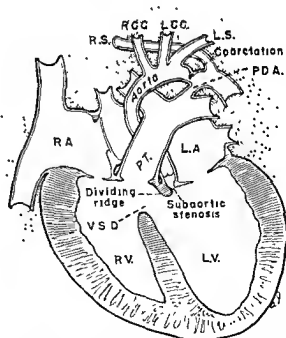


Figure VI-70. Diagrammatic representation of biventricular origin of pulmonary trunk with subaortic stenosis, reported by Becu and associates (1955). In this case a patent ductus arteriosus (P.D.A.) was present distal to coarctation of the aorta, and the right subclavian artery (R.S.) arose beyond the coarctation. (Reprinted by permission of the authors and C. V. Mosby Co.)

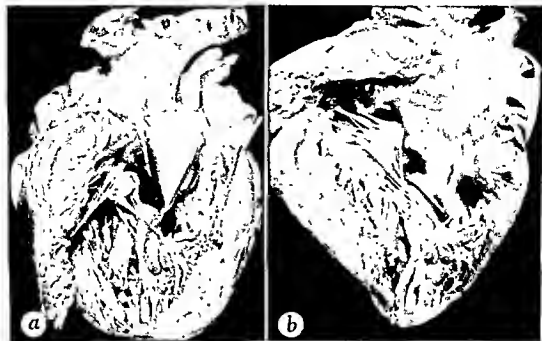


Figure VI-71. Origin of both great vessels from the right ventricle.

a. The aorta and pulmonary trunk have been opened. Beneath the pulmonary valve is an infundibular tract.

b. The ventricular septal defect contains a probe. The aortic origin within the right ventricle is clearly defined as is the orifice of the subpulmonary tract.

may be either "mitral" stenosis or insufficiency, usually the latter.

The other contralateral lesion that has been observed is subpulmonary stenosis. When this is present, the arrangement is essentially the same, but in mirrored image, as that in subaortic stenosis of normally disposed hearts (Cardell, 1956). Anderson and associates (1957) have emphasized the mirrored-image arrangement of the coronary arteries in corrected transposition. The coronary artery which rises from the right side of the aorta is the one which supplies the anterior descending coronary artery and the artery to the right atrio-ventricular sulcus. The coronary artery which occupies the position of the circumflex artery arises from the left side of the aorta and does not send a branch to the anterior aspect of the ventricular

septum. Anderson and associates pointed out that the peculiar arrangement of the coronary arteries may make right ventricular cardiomy a difficult problem.

The functional disturbances and clinical features in corrected transposition depend on associated malformations. The findings on cardiac catheterization may assist in a clinical diagnosis of corrected transposition of the great vessels (Helmholz *et al.*, 1958). Anderson and associates (1957) emphasized that angiocardiographic studies show the left margin of the great vessels to be formed by the aorta rather than by the pulmonary trunk. The occurrence of congenital heart block should lead to suspicion of corrected transposition of the great vessels with ventricular septal defect (Walker *et al.*, 1958).

PERSISTENT TRUNCUS ARTERIOSUS

Pathologic Anatomy. Persistent truncus arteriosus is characterized by the presence of but one arterial vessel leaving the ventricular part of the heart. There must not be a remnant, in fact or implied, of a second vessel. The coronary arteries and usually the pulmonary arteries arise from the ascending portion

of the single vessel, which then continues as the aorta. In an exceptional instance, pulmonary arteries are absent and, if the lungs are supplied by branches of the descending aorta and not by a patent ductus arteriosus, the condition may be regarded as a form of persistent truncus arteriosus.



Figure VI-72. Corrected transposition of the great vessels with atrial and ventricular septal defects in an 18-month-old male infant.

a. Right side of heart. The atrial septal defect at the fossa ovalis has been closed surgically. The right atrioventricular valve has the configuration of a normal mitral valve in mirrored image.

b. Right ventricle and pulmonary trunk. The smooth internal configuration of the right ventricle is representative of the features of a left ventricle in mirrored image. The anterior leaflet of the right atrioventricular valve is continuous with valvular tissue of the pulmonary valve. The ventricular septal defect, which has been closed by direct suture, lies immediately subjacent to the pulmonary valve.

c. Left side of heart. The atrial septal defect has been closed. The left atrioventricular valve has the configuration of a tricuspid valve in mirrored image. Short chordae attached to the septal and posterior leaflets may have made this valve incompetent.

d. Left ventricle and aorta. The mirrored image is portrayed of the outflow tract normally seen in the right ventricle. The ventricular septal defect is distant from the aortic valve and is overhung by tissue of the septal leaflet of the left atrioventricular valve. The coronary arteries arise from the aorta.

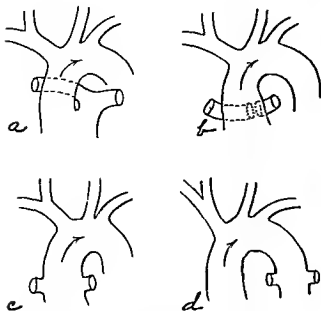


Figure VI-73. The four types of persistent truncus arteriosus. a. Type 1. b. Type 2. c. Type 3. d. Type 4. (From Collett and Edwards, 1949. Reproduced by permission of the W. B. Saunders Co.)

In 1949, Collett and the author reviewed the subject of persistent truncus arteriosus. Of a total of 116 cases, 80 were thought to be examples of *persistent truncus arteriosus* and 13 of *partial persistent truncus arteriosus*. Of the other 23 cases, 12 were not true examples of this entity even though they had formerly been so regarded by other authors. The remaining 11 cases could not be classified because of inadequate information as to the pulmonary arterial supply. The 80 cases of persistent truncus arteriosus were divided into four types, depending on the manner in which the lungs were supplied with arterial vessels. The characteristics of the four major types follow:

Type 1 (present in 48 per cent of 80 cases). A single pulmonary trunk and the ascending aorta arise from the truncus arteriosus (Figures VI-73a and VI-74).

Type 2 (present in 29 per cent of cases). The right and left pulmonary arteries arise close together from the dorsal wall of the truncus arteriosus (Figure VI-73b).

Type 3 (present in 10 per cent of cases). One or both pulmonary arteries arise independently from either side of the truncus arteriosus (Figure VI-73c).

Type 4 (present in 13 per cent of cases). The pulmonary arteries and the ductus arteriosus are absent. The sixth aortic arches are apparently absent. The arterial circulation to the lungs is fur-



Figure VI-74. Persistent truncus arteriosus, Type 1. The right ventricle has been opened to show the origin of the persistent truncus arteriosus from both ventricles above a septal defect. A short pulmonary trunk gives rise to the right and left pulmonary arteries. (From Dry, T. J., and associates. *Postgraduate Medicine*, 4:327 [1948]. Reproduced by permission of the authors and *Postgraduate Medicine*.)

nished by the bronchial arteries (Figure VI-73d).

Manhoff and Howe (1949) gave a comprehensive discussion of persistent truncus arteriosus. They reported a case which, according to the foregoing classification, would be designated as persistent truncus arteriosus, Type 4. They preferred to designate the condition *absence of the pulmonary artery*. They argued correctly that the absence of the right and left pulmonary arteries must be interpreted as indicating either absence or early involution of the sixth aortic arches. They also argued that the failure of the embryonic truncus arteriosus to be partitioned into pulmonary trunk and aorta was secondary to the deficiency of the sixth aortic arches. This interpretation, however, need not be correct. It is also possible that absence of the sixth aortic arches and failure of the truncus arteriosus to be partitioned were two independent conditions. Man-

hoff and Howe thought that in their case the truncus arteriosus had failed to be partitioned. Any other view is untenable. Yet they preferred to designate the single vessel leaving the heart as the "aorta" rather than a "truncus arteriosus." While this vessel has the gross anatomic characteristics of the aorta, developmentally it represents the embryonic truncus arteriosus. This case, therefore, must be regarded as a form of persistent truncus arteriosus.

In persistent truncus arteriosus the ventricular septum is defective. As a rule, the defect involved only the membranous portion; but in almost one fourth of the cases the muscular portion of the septum also was completely absent, the heart exhibiting the characteristics either of *cor biloculare* or *cor triloculare batriatum*.

The truncus arteriosus usually arises from both ventricles superior to the ventricular septal defect but occasionally it arises from the right ventricle exclusively. Less often the truncus arises from the left ventricle alone. In the 80 cases of malformation classified by Collett and Edwards, the truncus arose from both ventricles (overriding septal defect) in 38; from the right ventricle in 16; from the left ventricle in 2; from a single ventricle in 19; and in 5, the source was unknown.

Number of cusps in the semilunar valve. Humphreys (1932), has advocated the criterion of four cusps in making the diagnosis of persistent truncus arteriosus. This criterion for morphologic diagnosis does not seem essential and gains little support from the developmental characteristics of the malformation. In 60 of the 80 cases which Collett and the author classified, there were data as to the number of valve cusps. In the majority (43 cases) the valve of the truncus was formed by three cusps; in 9 cases (all examples of Type 1), four cusps; in 6, three cusps one of which was partially divided; in 1, six cusps; and in 1, two cusps.

The coronary arteries arise from the truncus arteriosus. In 1 case there were three coronary arteries and in 7 cases a single coronary artery.

The aortic arch is frequently anomalous. In 80 cases of persistent truncus arteriosus a right aortic arch was present 11 times and a double aortic arch was present once (Kerwin, 1936). In the other 68 cases of persistent truncus arteriosus, it was either stated or assumed that the aortic arch was on the left side.

Absence of the ductus arteriosus. The ductus is absent in more than half of the cases. In Type 4, by definition, the ductus is always absent. The

ductus arteriosus may also be absent in the tetralogy of Fallot, in hearts with a single ventricle and occasionally in ventricular septal defect. Each of these malformations allows sufficient communication between the two circulations during fetal life so that the ductus is used little and, therefore, undergoes atrophy.

Incorrect Interpretation of Persistent Truncus Arteriosus. Of the 116 cases which Collett and the author reviewed, 12 did not seem to be *bona fide* examples of persistent truncus arteriosus. The characteristics of these cases were (1) origin from the heart of a single arterial trunk which followed the course of the aorta and (2) origin of the pulmonary arterial system from a ductus arteriosus. In 8 of these cases two pulmonary arteries arose from a patent ductus arteriosus. We excluded such cases from the designation of persistent truncus arteriosus for the following reasons: Since the right and left pulmonary arteries are derived from the proximal portions of the right and left sixth aortic arches, the presence of both of them presupposes that the proximal portions of the right and left sixth aortic arches were present at one time; since the right and left pulmonary arteries showed no connection with the truncus or a derivative of it, those parts of the sixth arches must have been present at one time but must have subsequently disappeared. Under these circumstances, it is impossible to state whether the sixth aortic arch had arisen from a truncus arteriosus or from a pulmonary trunk which had developed from partitioning of the truncus. This view is shared by Manhoff and Howe (1949).

In the patient with a right aortic arch reported by Hatrix (1926) the left lung was absent. The arterial supply to the right lung appeared to be by way of a right-sided ductus arteriosus. Thus interpreted, a right-sided pulmonary artery might have developed at one time but subsequently disappeared. In 3 cases a single arterial vessel arose from the heart but the pulmonary arterial supply arose from a right-sided ductus arteriosus connecting with the innominate artery (Herxheimer, 1910; Wood and Williams, 1928; Mehta and Hewlett, 1945). The type of case under discussion is removed from the category of persistent truncus arteriosus, since there is reason to believe that the truncus arteriosus had been partitioned but as a result of abnormality in this process the pulmonary trunk was so small as to escape detection.

Incidence. Fontana (1958), in a series of 357

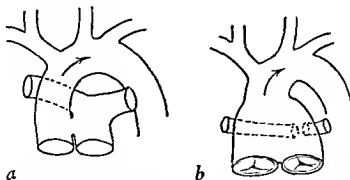


Figure VI-75. *a* Partial persistent truncus arteriosus (congenital communication between ascending aorta and pulmonary trunk) *b* Partial persistent truncus arteriosus with a large communication as in the cases of Bain and Parkinson (1943) and of Dadds and Hoyle (1949).

consecutive specimens of congenital malformations of the heart and great vessels in patients of all ages studied at the Mayo Clinic, found 6 instances of persistent truncus arteriosus.

Functional Disturbances and Clinical Features of persistent truncus arteriosus (see reviews of Taussig, 1947, and Anderson and associates, 1957) depend on the state of the pulmonary arteries. If the pulmonary arteries are wide, the derangements are like those in large ventricular septal defect without pulmonary stenosis. If the pulmonary arteries are absent or stenotic, the circulatory system functions essentially like that in the anatomic tetralogy of Fallot, with comparable degrees of obstruction to pulmonary flow. In patients with severe obstruction to pulmonary flow, cyanosis may be a paramount sign. In patients with malformation of Type 1, in whom the pulmonary arteries are wide, the major effects on the circulation are the result of a large left-to-right shunt. With cardiac catheterization, it may be difficult to distinguish persistent truncus arteriosus from more common malformations. A catheter passed above the semilunar valve, however, may yield features which will help in distinguishing persistent truncus arteriosus from malformations in which two great arteries arise from the heart. Angiocardiography may clearly delineate the pattern of the persistent truncus (Rowe and Vlad, 1953).

Complications and Prognosis. The complications of persistent truncus arteriosus depend to a great extent on the basic type of malformation. In patients with no significant obstruction to pulmonary flow, a large left-to-right shunt may cause left ventricular failure and pulmonary edema. When severe pulmonary obstruction exists, the complications are related to severe hypoxia. The

evidence indicates that the few patients who live to adult life are mainly those with severe pulmonary obstruction but with a well-developed bronchial blood supply to the lung.

Bacterial endocarditis is rare, probably because many patients die at an early age from other causes. This complication was encountered by Finley (1930) in a woman 22 years of age with a malformation of Type 4. A 19-year-old patient, with a similar malformation, died of a complication of parturition (Simon and Lustberg, 1951). The latter authors refer to other patients with persistent truncus arteriosus who lived to adult life. **Cerebral abscess** may complicate a right-to-left shunt (Hülse, 1918).

Partial Persistent Truncus Arteriosus (Congenital Aortic Septal Defect; Aorticopulmonary Septal Defect)

In *partial persistence* of the truncus arteriosus, the pulmonary and aortic channels are separated at the level of the semilunar valves, the ventricular septum is usually intact, but a localized defect in the septal system superior to the semilunar valves produces a communication between the ascending aorta and the pulmonary trunk (Figure VI-75).

This lesion may produce a *clinical picture* indistinguishable from persistent patency of the ductus arteriosus. Its pathologic anatomy and differential diagnosis have been reviewed (Potts *et al.*, 1949; Spencer and Dworken, 1950; Downing *et al.*, 1953; Giraud *et al.*, 1955). The lesion is amenable to surgical closure (Cooley *et al.*, 1957).

The localized defect is the result either of

absence of development of the truncocoanal septum at the level of defect or of localized fenestration of the septum after it has formed. Rarely there may be a large defect between the pulmonary trunk and the aorta, even though their respective semilunar valves are well formed and the ventricular septum is intact. The functional changes in partial persistence of the truncus arteriosus are quite different from those of complete persistence of truncus arteriosus.

Perelman and Putschar (1949) pointed out that from the *pathologic anatomy* it may be difficult or impossible to determine whether the communication is congenital or acquired. This is particularly true when the communication is encountered in an adult and when there is an inflammatory process at the margin of the communication. They reviewed 13 reported cases of communication between the ascending aorta and the pulmonary trunk and reported an instance in a newborn infant. While some of the patients died during infancy, 5 of the 13 lived to adult life, the oldest being 48 years of age at the time of death. Congestive cardiac failure was the cause of death in the older patients and in some of the children. Twelve of the 13 cases reviewed by them coincide with 12 of the 13 cases of partial persistent truncus arteriosus reviewed by Collett and Edwards (1949). Perelman and Putschar did not list the case of Bain and Parkinson (1943) which had an extensive communication between the aorta and the pulmonary trunk. The patient of Bain and Parkinson was a young man aged 18 years. Above

the cardiac ventricles was an ovoid aneurysmal sac, measuring 8 cm. in greatest dimension, which had 6 apertures. One orifice led to an arterial trunk from which arose the innominate, the left common carotid and left subclavian arteries, the second aperture led to the descending aorta, the third and fourth were dorsal and represented the ostia of the right and left pulmonary arteries, the fifth and sixth were caudal and communicated with the base of the aorta and of the pulmonary trunk. The aortic and pulmonary orifices were properly formed and each contained its respective valve. The ventricular septum had no defect. A similar condition was presented by the patient of Dadds and Hoyle (1949), a boy of 15 years who died of congestive cardiac failure. The pulmonary trunk was dilated to aneurysmal proportions and a large communication (6 by 5 cm.) with smooth edges was present between the ascending aorta and the pulmonary trunk. The ventricular septum was intact, and the aortic and pulmonary valves were normally formed.

In a case similar to that of Bain and Parkinson, the author encountered a heart with a patent ductus arteriosus, which had simultaneous rupture of the wall of the ductus and of the adjacent portions of the aorta and pulmonary trunk proximal to the ductus arteriosus. The resulting lesion left a large communication between the ascending aorta and pulmonary trunk. It is impossible to say whether cases like Bain and Parkinson's are examples of an aortic septal defect or of complicated patent ductus arteriosus.

DEXTROCARDIA

Definition. Lichtman (1931), who made an extensive review of the literature, defined dextrocardia as a condition in which the heart assumed a position in the right side of the thorax with its apex pointing to the right. It is a congenital malformation. Excluded from the category of dextrocardia are hearts that are situated on the right side by virtue of congenital or acquired disease in neighboring structures. *Isolated dextrocardia* is defined as dextrocardia in association with normal position of all the other viscera. Chapman and Gibbons (1950) adopted the classification of dextrocardia by Mandelstamm and Reinberg, which includes three types. The first type is associated with complete or partial situs inversus of other viscera. The sec-

ond and third types are examples of isolated dextrocardia. In the second type, the cardiac chambers show mirrored inversion, the arterial chambers being on the right and the venous chambers on the left. In the third type the cardiac chambers show a normal relationship, the venous chambers being on the right and the arterial chambers on the left.

Following an extensive review of the literature, Rosler (1930) concluded that *isolated dextrocardia is always associated with cardiac malformations*. Lichtman was of the same general opinion but stated that, in his review of 161 hearts with isolated dextrocardia, 3 hearts had no isolated cardiac defect. Brown (1939) referred to a case of Stevenson which likewise had no malformation

associated with the isolated dextrocardia. Even in the dextrocardia of situs inversus, cardiac malformations are common (Taussig, 1947). The malformations which are associated with isolated dextrocardia frequently include pulmonary stenosis or septal defects, and may include a variety of intricate deformities of the heart. Dry and associates (1948) reported isolated dextrocardia in an infant 10 months old who had a single ventricle.

Inasmuch as congenital malformations of the heart are common in isolated dextrocardia, *life expectancy* is often short. The average age at death is less than 30 years, many of the patients dying during the first year of life. An exceptional case is that of Ruskin and associates (1943). Their patient, a woman 55 years of age at the

time she was studied clinically, had had 7 pregnancies.

Transposition of the great vessels is commonly associated with isolated dextrocardia and in some cases the *transposition* is *corrected*. The aortic arch may cross ventral to the right bronchus, but usually it crosses over the left. The descending aorta usually is on the left side, regardless of the position of the aortic arch. The electrocardiographic features of isolated dextrocardia have been reviewed by Shepard and Stewart (1948) and by Burchell (1949).

Isolated levocardia or *isolated sinistocardia* is characterized by the heart and apex pointing to the left in patients with situs inversus. In these cases congenital malformations of the heart are probably as common as are malformations in patients with isolated dextrocardia.

SUBAORTIC STENOSIS



Figure VI-76. Subaortic stenosis in a man aged 26 years. *a*, The unopened fibrous collar in the outflow tract of the left ventricle. *b*, The unopened aortic orifice is viewed from above. The aortic valve is normal and beneath it is the subaortic stenosis.

Pathologic Anatomy. In subaortic stenosis the outflow tract of the left ventricle shows localized narrowing. Keith (1909) compared the stenosis of the left ventricular outflow tract in this condition to stenosis of ostium infundibuli of the right ventricle.

The most striking change in the fully established case is the thickened, gray and opaque endocardium of the outflow tract of the left ventricle. The lower margin of the thickened endocardium projects as a ridge or shelf facing caudally into the lumen of the left ventricle. This ridge, composed of elastic and collagenous tissue, not only involves that portion of the outflow tract of the left ventricle formed by the ventricular septum, but is also present on the neighboring ventricular surface of the anterior leaflet of the mitral valve. This appears to produce a stenosing fibrous collar in the left ventricular outflow tract (Figure VI-76*a*). In some descriptions of subaortic stenosis, this feature is the sole one mentioned.

Some defects show a peculiar bulge on the part of the ventricular septum (Greenberg and Simon, 1949), the ventricular septum extending farther to the left than normal and so into the path of the outflowing left ventricular blood. This is probably the underlying structural alteration. At other times, though the ventricular septum is intact, the base of the aorta lies more to the right

than normal. Rae's patient (1936) also had an aneurysm of the membranous portion of the ventricular septum.

The channel of the left ventricular outflow tract at the level of stenosis is usually so reduced in diameter as to admit only the examiner's little finger, in contrast with the normal caliber of the aortic valve (Figure VI-76b).

Typical features of this condition were clearly illustrated in 1875 by Lauenstein. A few reported cases have had aortic valvular malformations. Dilg in 1883 reported subaortic stenosis in a patient 2 years of age and reviewed 15 cases reported earlier, he stated that in his case and in Boulard's, the aortic valves were bicuspid. The case of Walsh and associates (1943) exhibited a large posterior and two smaller anterior aortic cusps. According to these authors, a bicuspid aortic valve was present in Thursfield and Scott's patient. In Dornmann's patient (1939), a laborer aged 16 years, the aortic valvular cusps were underdeveloped and composed of myxomatous tissue. In Case 1 of Morrison and Edwards (1950), the patient was a man aged 26 years who died of congestive cardiac failure and presented a patent ductus arteriosus associated with his defect. In a case observed by the author, a ventricular septal defect existed above the subaortic stenosis.

Incidence. In 1937 Wiglesworth stated that he was able to find only 36 cases of subaortic stenosis in the literature. Gruenwald (1947) reported on 6 cases which were found at necropsy at the Mt. Sinai Hospital of New York City over a period of 7 years. Gruenwald expressed the opinion that the condition is probably more common than is evident from the number of cases reported. Walsh and associates (1943) stated that no example of subaortic stenosis was found among more than 10,000 necropsies at the Massachusetts General Hospital in Boston. Nine examples of this condition were encountered among 357 examples of major cardiac and vascular malformations

in the pathologic collection of the Mayo Clinic.

Functional Disturbances. The chief functional disturbance of subaortic stenosis is strain of the left ventricle with resulting hypertrophy of its wall. This often causes increased cardiac weight (Greenberg and Simon, 1949).

Complications and Prognosis. Cardiac failure may cause death of the patient. Many of the patients live to adult life (Gruenwald, 1947) and in some the lesion is incidental to other unrelated diseases. There is great danger, however, of bacterial endocarditis.

This inflammatory process may originate on the rim of fibrous tissue (Gruenwald, 1947), presumably at the zone of greatest mechanical stress, or on the aortic valve (Wiglesworth, 1937; Mason and Hunter, 1942). In the patient of Walsh and associates, the bacterial endocarditis probably originated on the deformed aortic valve and involved the subaortic shelf and the mitral valve secondarily. In the second case of Morrison and Edwards (1950), bacterial endocarditis involved the aortic valve and the subaortic shelf of fibrous tissue (Figure VI-77). Though a decision could not be reached as to the site of origin of the infection, the inflammation was probably primary on the aortic valve. Dornmann's (1939) patient, a boy of 16, died suddenly.



Figure VI-77. Subacute bacterial endocarditis involving the aortic valve and the subaortic shelf in subaortic stenosis. From a man aged 25 years.

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Congenital Malformations

D. Malformations of the Valves

JESSE E. EDWARDS

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TRICUSPID ATRESIA

Pathologic Anatomy

IN TRICUSPID ATRESIA the heart functions as a two-chambered heart (Taussig, 1936; Blount *et al.*, 1951; Chiche, 1952; Astley *et al.*, 1953; Brown *et al.*, 1956). Although differences may exist from case to case, these hearts have the following anatomic features in common: (1) atresia of the tricuspid orifice (Figure VI-78), (2) patency of the atrial septum, and (3) a large mitral orifice leading into a large ventricular chamber.

No tricuspid orifice is present and usually no tissue is recognizable as that of the tricuspid valve. A depression or some localized fibrous thickening of the floor of the right atrium may be present at the expected location of the tricuspid orifice. In most cases, patency of the atrial septum is represented by retention of the fetal type of foramen ovale. An adequate channel leads from the right atrium into the left. As in the normal fetus, the valve of the foramen ovale is usually fully developed, but this is held away from the atrial septum by the column of blood which flows from the right atrium into the left. In cases of tricuspid atresia, this channel is usually the only outlet for blood entering the right atrium through the venae cavae and the coronary sinus. Less commonly, the

inferior part of the atrial septum is described as defective, and the region of the foramen ovale shows a normal postnatal condition. At times, the atrial septum is represented only by a rudimentary membrane which, because of its small size, is ineffective in partitioning the two atrial cavities. There is then, in effect, a single atrium. In the reported instances of tricuspid atresia, defects of the atrial septum, other than patency of the foramen ovale, are the exception rather than the rule.



Figure VI-78. Right atrium in tricuspid atresia. At the expected location of the tricuspid valve, there is neither orifice nor valvular tissue. Probe lies in patent foramen ovale.

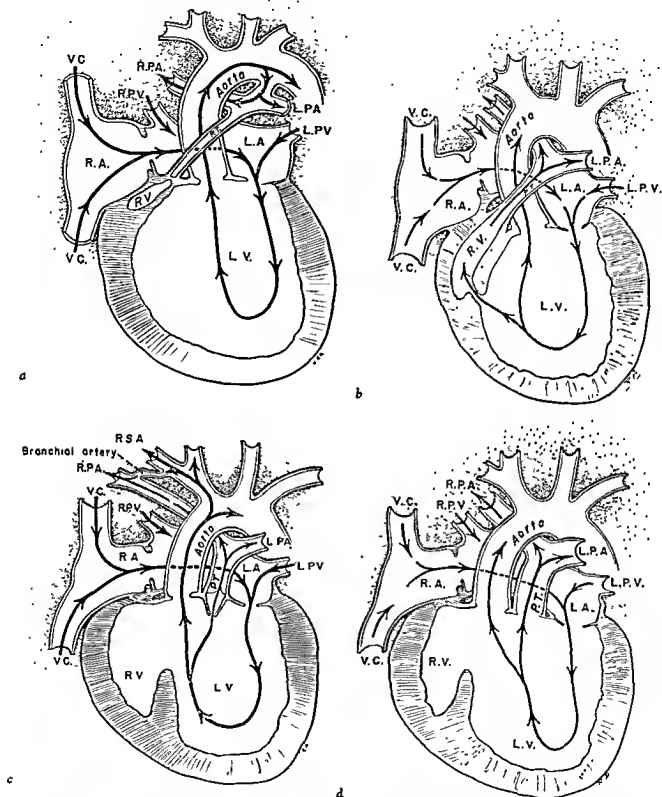


Figure VI-79. Four anatomic types of tricuspid atresia. *a*. Type Ia. Pulmonary atresia. Closed ventricular septum. No transposition of great vessels. *b*. Type Ib. Subpulmonary stenosis. No transposition of great vessels. *c*. Type IIa. Subpulmonary stenosis. Transposition of the great vessels. *d*. Type IIb. No pulmonary or subpulmonary stenosis. Transposition of the great vessels.

Commonly the right atrial chamber is wider than normal and its wall is thicker. Since all the incoming blood, both peripheral and pulmonary, ultimately collects in the left atrium, the latter chamber is usually wider than normal. Similarly, since all of the incoming blood must pass through the mitral orifice to enter the ventricular part of the heart, the mitral orifice is wider than one would find in a normal heart of a person of comparable age. Though its orifice is wider than normal, the mitral valve is normally formed and its leaflets are sufficiently developed to guard the left atrioventricular orifice adequately. In all cases of tricuspid atresia the mitral orifice leads into a large ventricular chamber from which all the blood circulating through the heart must pass on its way to the great arterial trunks.

The relation of the great vessels to each other and to the ventricular part of the heart varies in cases of tricuspid atresia. The varieties of interarterial relationships and ar-

terioventricular relationships constitute five groups, which form the basis for the anatomic classification of congenital tricuspid atresia presented in Table VI-2. This is a modification of the classification presented in 1949 by Edwards and Burchell who elaborated on the classification of Kuhne (1906).

TABLE VI-2

Congenital Tricuspid Atresia, Anatomic Classification
(Figures VI-79 to VI-84)

Type I. No transposition of great vessels

- a. Pulmonary atresia. Closed ventricular septum
- b. Subpulmonary stenosis
- c. No pulmonary or subpulmonary stenosis

Type II. Transposition of great vessels

- a. Pulmonary or subpulmonary stenosis
- b. No pulmonary or subpulmonary stenosis

TYPE IA. NO TRANSPOSITION OF GREAT VESSELS.
PULMONARY ATRESIA. CLOSED VENTRICULAR
SEPTUM

In this type of tricuspid atresia (Figure VI-79a), the left ventricle has a large capacity, its



Figure VI-80. Tricuspid atresia, Type Ib, in a female infant 3½ months old. a. The aorta is in free communication with the left ventricle. The probe lies in a narrow muscular tract leading from the left ventricle upward into a hypoplastic right ventricular chamber (see b.) (From Edwards, J. E.: *Postgrad. Med.*, 3:327-341, 1948. Reproduced by permission of *Postgraduate Medicine*.) b. The upper end of the probe shown in a lies in the hypoplastic right-sided ventricular chamber. The pulmonary orifice is in communication with the cephalic end of this chamber. The pulmonary valve is bicuspid. There is no transposition of the great vessels. (From Edwards, J. E., Dry, T. J., and Logan, G. B.: *Bull. Internat. A. M. Museums*, 28:34-42, 1948. Reproduced by permission of the *Bulletin of the International Association of Medical Museums*.)

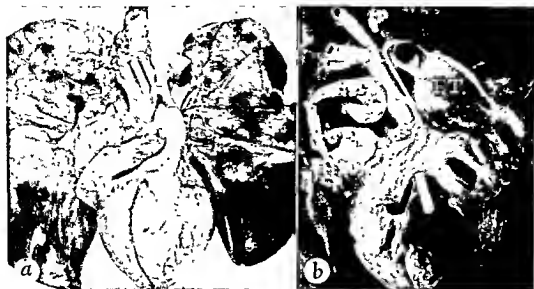


Figure VI-81. Tricuspid atresia, Type 1c, from a female infant 3½ years old. *a*. External view of heart and lungs. The great vessels are normally interrelated and there is no pulmonary stenosis. Focal pulmonary hemorrhage. *b*. Interior of common ventricle. The pulmonary trunk (PT) has been opened. The probe lies in the aorta. Specimen from case illustrated in Figure VI-78.

wall is thick, the ventricular septum is completely formed. The two ventricles are greatly disproportionate in size. The right ventricle is minute and lies virtually hidden in the superior portion of the right wall of the large left ventricle, its small size is explained by its failure to play any role in the circulation. It is merely an isolated endocardium-lined chamber, since both the tricuspid and the pulmonary valve orifices are atretic. Its very thin wall contrasts with the condition of the right ventricle in pulmonary atresia with intact ventricular septum and patency of the tricuspid orifice. The pulmonary atresia usually occurs at valve level, the pulmonary trunk superior to the valve level being hypoplastic but patent. The aorta and the pulmonary trunk are not transposed but are correctly interrelated. The ductus arteriosus is usually patent and constitutes the major channel by which the lungs receive blood (Elster, 1950).

**TYPE 1B. NO TRANSPOSITION OF GREAT VESSELS.
SUBPULMONARY STENOSIS**

This is the most common type of tricuspid atresia (Figures VI-79b and VI-80). The great vessels are correctly interrelated. The aorta is of normal caliber or wider than normal. The pulmonary trunk is somewhat narrower than normal but usually is of adequate caliber to carry a sufficient amount of blood to the lungs, were there no subpulmonary stenosis. In almost one half of the cases the pulmonary valve is bicuspid. Us-

ually this does not cause any pulmonary stenosis, but at times the configuration of the bicuspid valve is responsible for pulmonary stenosis (Crocker, 1879). Examination of the ventricular part of the heart reveals a large ventricular chamber into which blood flows through the mitral orifice. The large ventricular chamber communicates freely with the aorta (Figure VI-80a). In addition the large chamber communicates by means of a narrow tract, often described as being entirely muscular-walled, with a smaller narrow ventricular chamber (Figure VI-80b). The latter lies obliquely along the right superior aspect of the ventricular mass. In an occasional case, 2 openings are present between the 2 chambers (Bellet and Stewart, 1933; Grayzel and Tennant, 1934). The superior extremity of the small ventricular chamber communicates with the pulmonary orifice. The tract connecting the 2 ventricular chambers is usually narrow and constitutes the major barrier to the flow of blood from the larger ventricular chamber to the lungs. In addition, the diminutive size of the smaller ventricular chamber may constitute another cause of subpulmonary stenosis in this type of tricuspid atresia. At the time of death the ductus arteriosus is usually closed.

**TYPE 1C. NO TRANSPOSITION. NO PULMONARY
OR SUBPULMONARY
STENOSIS**

This type of tricuspid atresia is rare (Brinton

and Campbell, 1953). The author has observed a case in a young female infant. The type is characterized by normal relationship between the great vessels and absence of pulmonary or subpulmonary stenosis (Figure VI-81).

**TYPE IIa. TRANSPOSITION OF GREAT VESSELS.
PULMONARY OR SUBPULMONARY
STENOSIS**

Transposition of the great vessels is present (See Rogers *et al.*, 1950; Kroop, 1951). A small or diminutive ventricular chamber lies along the right side of the larger chamber and appears as a diverticulum thereof (Figures VI-79c and VI-82 to VI-84). There is some question whether there are two ventricles or a single one, from an anatomic viewpoint. Functionally, there is but a single ventricle. The pulmonary trunk arises dorsal to, and usually to the left of, the aorta. The two vessels ascend vertically parallel to each other. The pulmonary trunk arises from the large ventricular chamber, and its ostium is closely approximated to the anterior leaflet of the mitral valve which lies to the left of the subpulmonary region. A stenotic muscular tract which leads from the ventricle to the pulmonary trunk is the usual site of pulmonary stenosis in this type. Rarely the stenosis is at the pulmonary valve or in the pulmonary trunk (Lev and Saphir, 1937; Manhoff and Howe, 1945). In the author's case the subpulmonary tract was atretic.

**TYPE IIb. TRANSPOSITION OF GREAT VESSELS.
NO PULMONARY OR SUBPULMONARY
STENOSIS**

The malformation of this type (Figures VI-79d and VI-85) is identical with Type IIa in all respects, except for the state of the pulmonary circulation (see Robinson and Howard, 1948; Ross, 1952). In Type IIb the pulmonary trunk arises dorsal to the aorta as in Type IIa, but there is no pulmonary or subpulmonary stenosis.

Incidence

Tricuspid atresia is uncommon. In 6 of 357 specimens in the collection of the Mayo Clinic, Fontana (1958) found tricuspid atresia. In 1952 Chiche found 70 cases reported in the literature. According to the classification given above, the distribution of cases was as follows: Type Ia, 6 cases; Type Ib, 45; Type IIa, 10, and Type IIb, 9 cases. No cases of malformation of Type Ic were reported.

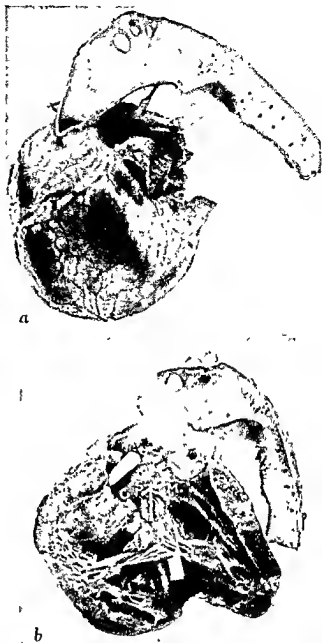


Figure VI-82. Tricuspid atresia, Type IIa, in a boy 12 years old. (From Edwards and Burchell, 1919. Reproduced by permission of the W. B. Saunders Company.) *a.* The unopened heart and the opened aorta. The aorta arises in an anterior transposed position. The pulmonary trunk lies behind the aorta and is hidden in a shadow. The ligamentum arteriosum extends from the left pulmonary artery to the aorta. *b.* The left ventricular chamber has been opened. The lower large probe lies in the mitral orifice. The upper large probe lies in the diminutive right-sided ventricular chamber. The small probe lies in the stenotic subpulmonary orifice, which is bordered by the crista supraventricularis (C.S.) on the right and the anterior leaflet of the mitral valve (M.) on the left. The transposed aorta is in free communication with both ventricular chambers. In spite of the appearance of two ventricular chambers, the free communication between the two cavities produces, in effect, a single ventricle.



Figure VI-83 Tricuspid atresia, Type IIa (Other illustrations of this case appear in Figures VI-82 and VI-84.) Close-up view of the outflow region of the ventricular part of the heart. Lying behind the opened orifice of the transposed aorta is the stenotic ventricular opening of the subpulmonary tract (tip of arrow). The tract is bounded by the crista supraventricularis (C.S.) on the right and the anterior leaflet of the mitral valve (M.) on the left. (From Edwards and Burchell, 1949. Reproduced by permission of the W. B. Saunders Company.)

Associated Conditions

Usually no significant malformations are associated with tricuspid atresia. Although anomalies of the aortic arch are common in some malformations, they are relatively uncommon in tricuspid atresia. A double aortic arch was described in the case of Van der Henst and associates (1953) in which the malformation was of Type IIa. In a clinical case without pulmonary stenosis, Astley and associates (1953) described a right aortic arch. In Case 2 of Huebschmann (1921), the ductus arteriosus ran between the right pulmonary artery and the innominate artery.

Juxtaposition of the Auricular Appendages was present in the case of Rogers and asso-

ciates (1950; Figure VI-84) and in 2 other cases of the Mayo Clinic collection. In 2, the malformation was of Type IIa and in the third, Type IIb. Enlargement of bronchial arteries occurs if the pulmonary blood flow is obstructed.

Functional and Clinical Features

The heart functions as though it were a two-chambered heart. In fact, it is likely that greater mixing of blood occurs in cases of tricuspid atresia than when a common atrioventricular valve exists, as in the true anatomic two-chambered heart. The crucial point in the functional behavior is the proportion of ventricular blood that is distributed to the lungs as compared to the systemic circulation. This in turn depends on whether pulmonary stenosis exists. (See discussion of Single Ventricle, page 337.) In general, patients with tricuspid atresia associated with pulmonary stenosis exhibit cyanosis and other manifestations that accompany cyanosis. In patients who do not have pulmonary stenosis, the major problems are those of pulmonary recirculation. When the interatrial communication is small, the right atrial and systemic venous pressure may be elevated and the veins may pulsate.

Roentgenographically, the shape of the left border of the heart in the frontal projection is the most important differential feature (Astley *et al.*, 1953). Concavity of the pulmonary segment, prominence in the upper part of the left lower segment and a vertical border below this, give the heart a characteristic square shape. *Angiocardigraphy* reveals the abnormal pathway of blood across the atrial septum and simultaneous filling of the great arteries. The dye-dilution curves recorded in a peripheral artery are similar whether the dye is injected into the left atrium or into the left ventricle. The right ventricle cannot be entered from the right atrium. The *electrocardiogram* is helpful in most cases and classically shows left axis deviation (Rihl *et al.*, 1929); in some cases, however, no axis deviation is identified (Casal *et al.*, 1950, Kroop and Grishman, 1950; Sommers and Johnson, 1951). In 1 case the electrocardiogram showed complete heart block (Dickson and Jones, 1948).

Prognosis

Patients with Type Ia rarely, if ever, survive infancy. Among the 28 cases of Type Ib which were reviewed, the longest survival was

4 years, the shortest, 10 hours; and the mean age at death, slightly more than 7 months.

Patients with Type IIa have the longest survival. In this group belongs the frequently quoted case of Hedinger (1915) of a woman who died at the age of 56 years after leading an active life. The patient of Rogers and associates (1950) died at the age of 12 years. Patients with tricuspid atresia of Type Ic or IIb usually die in early infancy.

Developmental Basis

Three different phenomena have been cited to explain the occurrence of tricuspid atresia: (1) abnormality of atrial septum, (2) abnormality of ventricular septum, and (3) fetal endocarditis.

The view of Monckeberg was that tricuspid atresia is caused by maldirection of growth of the atrial septum. This hypothesis has been logically attacked by Scriba (1937) who pointed out that, in most of the cases of tricuspid atresia, evidence of abnormal direction of growth of the atrial septum is either absent or not proved. Scriba pointed out examples of misplacement of the atrial septum without atresia of either of the ventricular ostia. Furthermore, in certain cases of tricuspid atresia the atrial septum is incompletely formed, its lower margin hanging unattached. It seems reasonable to assume that, at least in some cases, Monckeberg's explanation is not tenable.

Instances of atresia of the tricuspid orifice, in which 2 ventricles are present, constantly show a large left ventricle and a small right ventricle so that the ventricular septum is eccentric. The superior portion of the septum often lies close to the expected position of the tricuspid orifice, so that the question may be raised whether the eccentric ventricular septum is responsible for the closure of the tricuspid orifice. It should be emphasized that the position of the ventricular portion of the heart is logically the result of the abnormal circulatory conditions produced by the tricuspid atresia, rather than the cause of that anomaly. Further evidence against the view that tricuspid atresia is caused by an eccentric ven-

tricular septum is supplied by cases of isolated pulmonary atresia, in which the left ventricle is large, the right ventricle is small, and the ventricular septum is eccentric. In these cases, tricuspid atresia need not be associated. Farber and Hubbard (1933) have furnished evidence to support the thesis that certain instances of valvular stenosis and atresia are the result of fetal endocarditis. They believe that anomalies which result from such inflammation occur in rather late stages of cardiac development. On this basis, it is conceivable that tricuspid atresia, Type Ia, might result from an inflammatory process, but such an explanation would seem inappropriate for other types of this malformation.



Figure VI-84. Tricuspid atresia, Type IIa. (Other illustrations of this case appear in Figures VI-82 and VI-83.) The stenotic subpulmonary tract has been opened. The tract is bounded on the right by the crista supraventricularis (C.S.) and on the left by the anterior leaflet of the mitral valve (M.). P.V. indicates one leaflet of a bicuspid pulmonary valve, P.T., pulmonary trunk. The right atricular appendage (R.A.) is in an abnormal position, lying to the left of the pulmonary trunk. A similar abnormal position of the right atricular appendage was described in the second case of Huebschmann (1921). (From Edwards and Burchell, 1949. Reproduced by permission of the W. B. Saunders Company.)

EBSTEIN'S MALFORMATION OF THE TRICUSPID VALVE

Pathologic Anatomy

Externally the heart in Ebstein's malformation of the tricuspid valve usually has a char-

acteristic appearance. The right ventricular chamber is unusually large and may bulge perceptively above the rest of the cardiac sur-

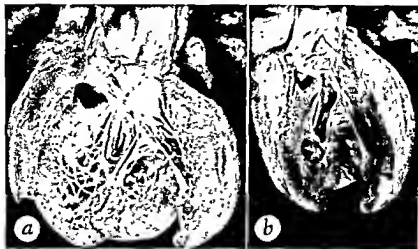


Figure VI-85. Tricuspid atresia, Type IIb. *a*. Common ventricle and pulmonary trunk. The transposed pulmonary valve is continuous with the underlying anterior leaflet of the mitral valve. Beneath the pulmonary valve and in front of the mitral valve is a tract leading to the transposed aorta seen in *b*. *b* Common ventricle, subaortic tract and transposed aorta.

face, particularly in the outflow portion of the right ventricle. The great vessels are probably interrelated, although the pulmonary trunk often appears narrower than the aorta. The essential disturbance consists in attachment of only a portion of the tricuspid valvular tissue proximally to the annulus fibrosus, while the remainder of the tricuspid valvular tissue attaches below this level (Figure VI-86). The functioning valvular tissue is usually composed only of the anterior leaflet and at times a portion of the posterior leaflet, the septal leaflet and varying amounts of the posterior leaflet, in effect, being nonfunctional. The basal attachment of the malformed elements is considerably below the annulus fibrosus, and the sites of their distal attachments vary frequently. They may be adherent entirely, or attached by anomalous multiple chordae, to the apical portion of the right ventricle. The large anterior leaflet is potentially functional. Because of the downward displacement of elements of the tricuspid valvular tissue, a considerable portion of the right ventricular chamber is anatomically continuous with the right atrium. Thus, in this condition the receiving chamber is large, while the propelling portion of the right ventricle, that part lying beyond the attachments of the tricuspid valve, is correspondingly small. The propelling portion of the right ven-

tricle is composed of the outflow tract and varying amounts of the inflow portion. At times, the right ventricular chamber has a recess beyond the apical attachment of the anomalous valvular tissue. A patent foramen ovale is often present, but occasionally the atrial septum is intact. The remaining valves are normally developed.

Occasionally, the basal portions of the septal and posterior leaflets are attached to the right ventricular wall at a short distance below the annulus fibrosus while the remainder of the attachments of the valve, including those of the chordae, are normal. Such *partial forms of Ebstein's malformation* may cause incompetence of the tricuspid valve. Sometimes a malformation resembling Ebstein's malformation of the tricuspid valve is seen in mirrored image in the left atrioventricular valve, as in corrected transposition of the great vessels (page 363; Edwards, 1954; Becu *et al.*, 1955).

In fully developed forms of Ebstein's malformation, the right ventricular muscle commonly is atrophic and the chamber correspondingly dilated. The atrophy may be both proximal and distal to the tricuspid valve, although usually it is most affected distal to the valve. The atrophy is regarded as probably secondary to the functional disturbances caused by the anomalous valve. In the heart of a newborn which the author observed, no atrophy was apparent. A ventricular septal defect is rare (Kilby *et al.*, 1956).

Incidence

Ebstein's malformation is uncommon. The collection of more than 550 pathologic specimens of malformations of the heart and great vessels, from persons of all ages in the Mayo Clinic, contains 5 examples of the classic variety of Ebstein's malformation. In 3 additional specimens, Ebstein's type of malformation was present in the left atrio-ventricular valve in association with corrected transposition of the great vessels. Minor forms of Ebstein's malformation also existed in 2 additional specimens in which the base of the septal leaflet and a portion of the adjacent posterior leaflet were attached slightly below the annulus fibrosus, and the remainder of the valvular attachment was essentially normal. In reviews of the literature, Kilby and associates (1956) and Jedlička and Schwartz (1957) found 71 and 72 cases, respectively, including their own material.

Functional and Clinical Features

The essential features (Engle *et al.*, 1950;

Blacket *et al.*, 1952; Lenègre *et al.*, 1955; Brown *et al.*, 1956; Kilby *et al.*, 1956; Jedlička and Schwartz, 1957) appear to be inefficient function of the right ventricle and, when an interatrial communication is present, a right-to-left shunt at the atrial level (Brown *et al.*, 1956). The pulmonary pressure is normal, and the histologic appearance of the pulmonary vessels is normal (Brown *et al.*, 1956). The function of the tricuspid valve varies. While its caliber is reduced compared to that of a normal tricuspid valve, there usually is no differential in pressure across this valve to indicate stenosis. Some patients show suggestive signs of tricuspid insufficiency, but usually the valve is competent. During diastole the large functioning leaflet may possibly obstruct that portion of the right ventricle which lies as a recess beyond the anomalously adherent valvular tissue (Kilby *et al.*, 1956). During ventricular systole, when the recess becomes filled, blood would be prevented from entering the pulmonary trunk. Engle and associates suggested that the chamber of the functioning right ventricle is so small that

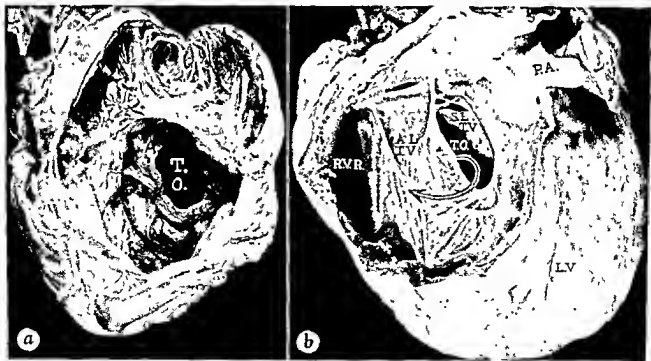


Figure VI-86. Ebstein's malformation of tricuspid valve. *a.* Right atrium and ventricle from above. The septal and posterior leaflets of the tricuspid valve are anomalously attached to the apical portion of the right ventricle. The anterior tricuspid leaflet, a portion of which is shown (*A.*), is normally attached. The tricuspid orifice (*T.O.*) is reduced in size by the anomalous attachment of the valve leaflets. *b.* Right ventricle and pulmonary trunk. The tricuspid valve is unopened, the anterior leaflet and a portion of the posterior leaflet of the tricuspid valve form a large curtain (*A.L.T.V.*). The arrow indicates that during ventricular diastole the curtain moves toward the right ventricular wall. During ventricular systole this leaflet flaps up toward the orifice of the common receiving chamber. The changing position of the large functioning leaflet is responsible for dissipation of right ventricular energy. *P.A.* indicates pulmonary artery; *S.L.T.V.*, septal leaflet of tricuspid valve; *T.O.*, tricuspid orifice; *R.V.R.*, right ventricular recess; *L.V.*, left ventricle. (Reproduced from Kilby *et al.*, 1956. With permission of Medicine.)



Figure VI-87 Left atrium in mitral atresia. No valvular tissue is present. *a.* From a male infant 21 months of age. The interatrial communication (point of arrow) is tiny. Thebesian veins are enlarged. *b.* From a girl 14 years old. The interatrial communication (point of arrow) is narrow but wider than in *a.*

improper filling of the right ventricle may be a cause of cardiac dysfunction. Since an interatrial communication is common in this condition, a right-to-left shunt is frequent, and varying degrees of desaturation of the systemic arterial blood result. In some instances this is sufficient to cause cyanosis.

A variety of murmurs, or no murmurs, may be heard. The most characteristic sign is a *third heart sound* (Medd *et al.*, 1954; Brown *et al.*, 1956; Kilby *et al.*, 1956). The *electrocardiographic abnormality* is usually called right bundle-branch block but may actually represent late activation of the supraventricular or atrialized portion of the right ventricle (Kilby *et al.*). In a case with conduction defects of the Wolff-Parkinson-White type, Lev and associates (1955) found anomalous muscular pathways between the atrial and ventricular portions of the myocardium. In other instances when such anomalous pathways were identified, the Wolff-Parkinson-White syndrome was not encountered (Edwards, 1953). Cardiac arrhythmias are frequent, and include paroxysmal supraventricular tachycardia, premature atrial and ventricular extrasystoles, atrial flutter, and atrial fibrillation.

Roentgenographically, the postero-anterior view shows an enlarged, usually globular heart with a vascular pedicle of normal size. Angiocardiographic study often shows evidence of a right-to-left shunt at atrial levels, delayed emptying of the

right side of the heart, and poor visualization of the pulmonary vascular tree. Studies by cardiac catheterization are of significance when the change from right atrial to right ventricular pressure occurs at a considerably lower level than one would anticipate in the normally formed heart.

Following the prediction of Engle and associates (1950), many cases of Ebstein's malformation have been diagnosed clinically (Reynolds, 1950; Soloff *et al.*, 1951; Van Lingen *et al.*, 1952; Broadbent *et al.*, 1953; Henderson *et al.*, 1953; Bayer *et al.*, 1954; Göttsche and Fallholt, 1954; Kerwin, 1955; Brown *et al.*, 1956).

Differential Diagnosis

Among patients with cyanosis, the more common varieties of cyanotic congenital heart disease must be considered, including pulmonary stenosis with intact ventricular septum and atrial communication. The findings on cardiac catheterization are diagnostic, and angiocardiographic features are helpful. In the presence of cyanosis, the absence of pulmonary hypertension is suggestive of Ebstein's malformation.

Complications and Prognosis

The variety of complications that may develop include sudden unexplained death, congestive heart failure, cerebral abscess without bacterial endocarditis, and paradoxical embolism in the systemic circulation (Kilby *et al.*, 1956). Some pa-

tients with Ebstein's malformation die in infancy but most survive to adult life. The average age at death in the cases reviewed by Kilby and asso-

ciates was 22 years, the oldest patient being 61. Adams and Hudson (1956) reported survival of a patient to the age of 79 years.

TRICUSPID STENOSIS; TRICUSPID INSUFFICIENCY

Congenital tricuspid stenosis is rare, being less common than tricuspid atresia (Herxheimer, 1910).

Peacock (1853) described an instance in a female infant, aged 2 months, who had had dyspnea and cyanosis. The tricuspid valve showed a diaphragm-like fusion of the leaflets which was thought to be congenital rather than acquired. In addition, the ventricular septum had two defects. Lewis (1945) described a case of congenital tricuspid stenosis in a 3-day-old female infant. The tricuspid leaflets showed focal thickenings, which on microscopic examination were composed of collections of cellular connective tissue. The mitral valve was grossly normal but showed essen-

tially the same microscopic picture as the stenotic tricuspid valve. Lewis concluded that the basis of the tricuspid stenosis was developmental rather than inflammatory.

Congenital tricuspid insufficiency also is rare.

In 1956 Barnitt and Ulrich described this malformation in a man of 28 who died from congestive heart failure, and reviewed 6 other cases in the literature. The essential developmental disturbance may be adherence of the posterior and septal leaflets of the tricuspid valve to the right ventricular wall, somewhat in the manner of unusual attachments seen in Ebstein's malformation.

MITRAL ATRESIA

Congenital mitral atresia is a rare malformation usually causing death of the patient

during early infancy (Brockman, 1950, Large, 1950). Mitral atresia may be the only basic

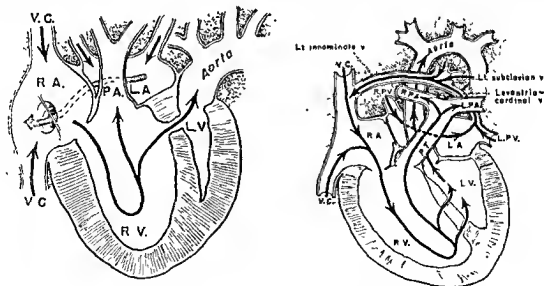


Figure VI-88. *a*. Intracardiac circulation in mitral atresia in a male infant 4 months old. A patent foramen ovale is the outlet for the left atrium. There is a ventricular septal defect. The transposed aorta arises from a small left ventricular chamber. (From Edwards, J. E.: *Postgrad. Med.*, 3:327-341, 1948. Reproduced by permission of *Postgraduate Medicine*.) *b*. Mitral atresia in a female infant 21 days old. In contrast to the usual situation in this malformation as shown in *a*, the foramen ovale is closed. An anomalous vein (levoatriocardinal vein) runs between the left atrium and the left innominate vein. In this way, left atrial blood flows toward the right atrium. The great vessels are not transposed. The two ventricles communicate by means of defects in the muscular part of the ventricular septum. (From Edwards and DuShane, 1950. Reproduced by permission of *Archives of Pathology*.)

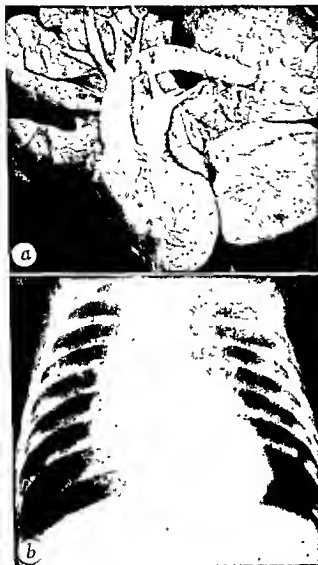


Figure VI-89. Mitral atresia with transposition of the great vessels in a male infant 3 months old. *a* Ventral view of exterior of the heart, great vessels and portions of the lungs. The ligamentum arteriosum extends in a normal way from the left pulmonary artery to the aorta. The great vessels are transposed, the aorta arising ventral to and slightly to the right of the pulmonary trunk. The left auricular appendage lies beside the pulmonary trunk. In this case, there was a common ventricle. The descending aorta has been deflected in front of the left lung. *b* Roentgenogram of the thorax in the case of mitral atresia illustrated in *a*. The right atrial shadow is wide. The prominent shadow at the left side of the base of the heart is probably caused by the left atrium.

malformation in a given case or may be associated with atresia of the aortic orifice (see page 400).

Pathologic Anatomy

The mitral orifice usually is represented by a blind depression when viewed from the left atrial

aspect, and no elements of valvular tissue are identifiable (Figure VI-87). In a case seen by the author, the mitral cusps were fused to form an atretic fibrous pouch. The left atrium often is smaller than normal, as in Wenner's case (1909). The chief outlet for blood coming into the left atrium from the pulmonary veins is a patent foramen ovale (Figures VI-87*b* and VI-88*a*). At times, the thebesian veins in the atrial septum are wider than normal and may carry some blood from the left atrium into the right. This route, however, must be of minor importance. The appearance of the patent foramen ovale is usually quite characteristic. The valve of the foramen ovale seems to be normally formed so that it would normally prevent left atrial blood from flowing into the right atrium. Probably as a consequence of the great pressure which is built up within the left atrium, the valve of the foramen ovale is forced through the foramen ovale into the right atrium, thus creating a peculiar type of patency.

In the patient of McIntosh (1926), the foramen ovale was prematurely closed, thus preventing the flow of blood across the atrial septum. An anomalous vein ran between the left atrium and the superior vena cava, thereby allowing an indirect communication between the left atrium and the right. In a case of this type encountered by Edwards and DuShane (1950), the anomalous vein ran from the left innominate vein to the left atrium (Figure VI-88*b*). In all cases of mitral atresia, the blood returning to the heart from the lungs ultimately reaches the right atrium. At the same time, the right atrial chamber receives, in a normal manner, blood from the venae cavae and the coronary sinus; thus, the right atrial chamber is usually greatly dilated and its wall hypertrophied. The tricuspid orifice represents the only communication between the atrial part of the heart and the ventricles.

The structure of the ventricular part of the heart varies in cases of mitral atresia. The most common form is that with but one ventricle (McIntosh, 1926; Scriba, 1937; Walls, 1941; Bergman and Morales, 1948). Other cases have had one or several ventricular septal defects (Edwards and Rogers, 1947). When a single ventricle is present, the great vessels are usually transposed (Figures VI-89 and VI-90*a*), but rarely, no transposition exists (Figure VI-90*b*). Lam and co-workers (1953) reported mitral atresia associated with ventricular septal defect and pulmonary atresia. In 2 similar cases seen by the author, 1

had in addition an anomalous connection of the right pulmonary veins, while the other had atresia of the larynx.

The course and relations of the great arteries leading from the heart vary. If a common ventricle is present, the great vessels are usually transposed. The patient of Bergman and Morales (1948), an infant 5½ months old, had a common ventricle but the great vessels were not transposed. In the case of Cree (1956), persistent truncus arteriosus was associated.

Incidence and Sex Distribution

In an extensive review of the literature, Brockman (1950) found 48 cases of mitral atresia. The collection of the Mayo Clinic of more than 550 hearts with congenital anomalies has 13 examples of mitral atresia. The incidence of male to female patients is about 3:2 (Brockman, 1950).

Functional and Clinical Features

Functionally, mitral atresia creates in essence a two-chambered heart. Since the pulmonary trunk

is usually of normal width, it might be expected that the adequate arterial channel to the lungs would prevent cyanosis. Cyanosis may, however, be present, and may be explained on the basis of pulmonary stenosis with impaired venous return from the lungs. It seems reasonable to assume that enlargement of an opening in the atrial septum, or the creation of an opening in the atrial septum if none exists, would relieve the barrier to venous flow from the lungs, and so remove the basis for cyanosis.

Prognosis

In his review of the literature, Blockman (1950) found that 65 per cent of the patients with mitral atresia were dead by 1 month of age. Of 41 cases reviewed, only 2 patients lived more than 10 years. The author has observed 2 patients who lived unusually long, one 14 years, and the other 15 years.

Developmental Basis

The developmental basis for mitral atresia is

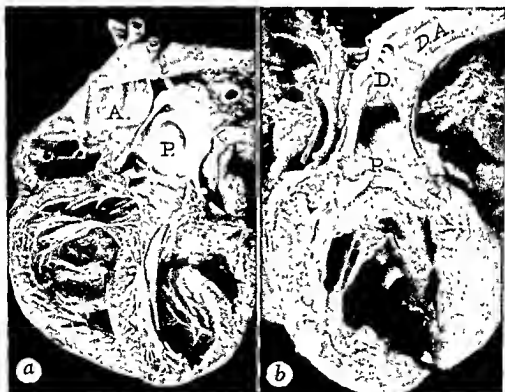


Figure VI-90. Ventricular portions of heart and great vessels in 2 cases of mitral atresia. *a.* The ventricular portion of the heart is a common ventricle. The great vessels are transposed, the aorta (A.) lying anterior to the pulmonary trunk (P.). No pulmonary or subpulmonary stenosis exists. From a male infant 21 months old whose left atrium was illustrated in Figure VI-87*a.* *b.* Both the aorta and the pulmonary trunk arise from a common ventricle. Great vessels are correctly interrelated. The origin of the pulmonary trunk (P.) is shown in this perspective. The aortic arch is hypoplastic and a patent ductus arteriosus (D.) communicates with the descending aorta (D.A.). (Specimen contributed by Dr. Ralph Knuseley.)

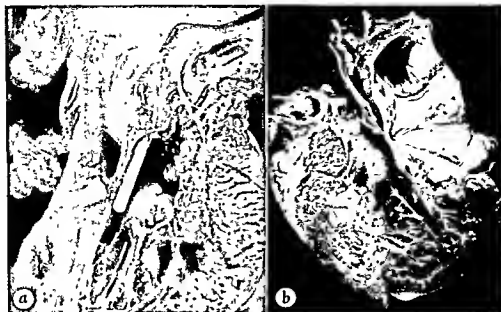


Figure VI-91 Mitral stenosis *a* From a child 4 days old who also had a ventricular septal defect, tubular hyperplasia of the aortic arch and bicuspid aortic valve. The mitral valve is viewed from below. The valvular tissue is fused to form a funnel-shaped structure. Probe in orifice. *b* From a male infant 1 year old. Sagittal section of left atrium, left ventricle and aortic valve. The mitral valvular tissue is thickened and the chordae shortened. A jet lesion lies on the ventricular septum opposite the mitral orifice. The left atrium is dilated. No malformation was associated in this case.

poorly understood (Brockman, 1950). The hypotheses concerning the origin of tricuspid atresia

are also applicable to mitral atresia (see Tricuspid Atresia, page 381).

MITRAL STENOSIS

Pathologic Anatomy

Congenital mitral stenosis resembles stenosis of rheumatic origin. Fibrous thickening of the leaflets, commissural fusion, and chordal shortening and fusion convert the valve into a funnel-shaped structure (Figure VI-91). Rarely multiple perforations in one membrane represent fusion of both leaflets (Swan *et al.*, 1949). Differentiation from acquired mitral stenosis may be difficult and often is made on the basis of the young age of the patient, absence of inflammatory stigmata, and association of other malformations. The left atrial cavity may be enlarged. The wall is hypertrophied, and the endocardium is greatly thickened. Classically the left ventricular endocardium is not thickened. Mitral stenosis, however, may be part of endocardial sclerosis in which, by definition, left ventricular endocardial thickening is present. The

pulmonary muscular arteries and arterioles show medial hypertrophy.

In a review of 34 cases from the literature and of 9 from the Children's Memorial Hospital, Montreal, Ferencz and associates (1954) noted that other cardiovascular malformations were commonly associated. Only 8 of the 43 cases reviewed had no associated defect. The commonly associated malformations of significance are patent ductus arteriosus, aortic valvular stenosis, and coarctation of the aorta. Septal defects are uncommon, only 2 cases of ventricular septal defect and none of atrial septal defect being encountered.

Incidence

Congenital mitral stenosis is uncommon; Ferencz and associates (1954) found only 34 cases in the literature since 1840. Their 9 cases were encountered among 210 specimens of cardiac malformations in children. Only 2 specimens are present in the collection of the Mayo Clinic

of more than 550 instances of cardiac malformations from patients of all ages.

Functional and Clinical Features

The functional derangements are identical to those of acquired mitral stenosis (Ferencz *et al.*, 1954). Elevation of pressure in the left atrium and pulmonary veins and capillaries is characteristic. Symptoms may be nonspecific. Common findings include failure to gain in weight and frequent respiratory infections, the latter probably following complicating pulmonary edema. Murmurs may be absent, when heard, they are not usually characteristic of acquired mitral stenosis. Electrocardiographically, right ventricular hypertrophy is present. Cardiac catheterization

reveals elevated pulmonary arterial "wedge" pressures and angiocardiology shows delayed emptying of the left atrium. If a patent ductus arteriosus coexists, a right-to-left shunt may occur and lead to cyanosis of the lower part of the body.

Differential Diagnosis

The clinical features may be duplicated (1) by other conditions causing obstruction of pulmonary venous flow (cor triatriatum; stenosis of individual pulmonary veins) and (2) by conditions causing left ventricular failure, including patent ductus arteriosus, endocardial sclerosis, aortic coarctation and ventricular septal defect (Edwards, 1954). The complexities in the diag-

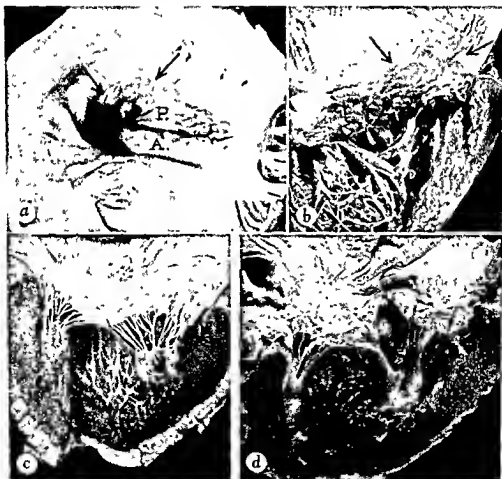


Figure VI-92. Mitral insufficiency. *a* and *b*. From a girl 5 years old who also had ventricular septal defect. *a*. Unopened mitral valve from above. Above the posterior leaflet of the mitral valve (*P.*) jet lesions (points of arrows) lie on the posterior wall of the left atrium. Accessory commissures in the posterior leaflet should be noted. (*A.* indicates anterior leaflet of mitral valve.) *b*. The mitral valve has been opened. The jet lesions on the left atrial wall are between the points of the arrows and above an extra commissure in the posterior leaflet. *c*. Opened mitral valve of normal heart for comparison with *d*. *d*. The posteromedial commissure of the mitral valve shows anomalous insertion of chordae into the basal portion of the left ventricle rather than into the posterior papillary muscle. The valvular tissue is displaced upward on each side of the commissure. A systolic murmur during life was probably the result of mitral insufficiency at this site.



Figure VI-93. Double orifice of the tricuspid valve. The chordae tendineae extend to the margins of an opening in the posterior leaflet of the tricuspid valve. Papillary muscles attach to the caudal extremities of the chordae tendineae. From a man 60 years old.

nosis are compounded by coexistence of some of the conditions from which mitral stenosis is to be distinguished.

Complications and Prognosis

The major complications are right ventricular

failure or pulmonary edema with or without secondary pneumonia. The outlook for life is poor. Of the 43 patients with this condition reviewed by Ferencz and associates, only 1 lived beyond 3 years of age.

MITRAL INSUFFICIENCY

Mitral insufficiency in association with congenital cardiac disease is relatively common. It may (1) complicate some conditions, (2) be part of complex malformations, or (3) appear as an independent condition (Edwards, 1954). As a complication of other conditions, it may be observed when the left ventricle is markedly enlarged as in left-to-right shunt, for example, in ventricular septal defect. At other times, it may coexist with ventricular septal defect and result from maldevelopment of the valve. This is characterized by anomalous insertion of the chordae from the posterior leaflet. Isolated collections of chordae insert into commissure-like formations in this leaflet (Figure VI-92*a* and *b*). Above the accessory commissures the posterior wall of the left atrium shows "jet" or "regurgitant" lesions. These are anatomic evidence of valvular incompetence. Most commonly, when mitral insufficiency is part of a complex malformation, it is part of a persistent common atrio-

ventricular canal (page 263).

In the section dealing with corrected transposition of the great vessels (page 361), it was pointed out that associated incompetence of the left atrioventricular valve is common. The incompetence may result either from anomalous insertion of chordae or from coexistence of a valvular malformation which is the mirrored image of Ebstein's malformation of the tricuspid valve in normally disposed hearts. Hearts with endocardial sclerosis (page 417) may show involvement of the mitral valve which produces either stenosis or incompetence. The latter seems to result from major shortening of the chordae. Occasionally, anomalous insertion of mitral chordae with mitral insufficiency may be present in otherwise normally developed hearts (Figure VI-92*c* and *d*); in a rare instance, a cleft may be present in the anterior leaflet of the mitral valve, as in persistent common atrioventricular canal, and may be related to it developmentally. No septal defects are associated, however.

DOUBLE ORIFICE OF THE MITRAL OR TRICUSPID VALVE

In these conditions, if the heart is viewed in the conventional manner, the opening is usually seen in the anterior leaflet of the mitral valve or in the septal leaflet of the tricuspid valve. Attached to the margins of the defect are chordae tendineae, and the latter in turn attach to papillary muscles (Figure VI-93). The extra opening probably has competent valvular function, and the condition has more interest from a developmental than from a pathologic point of view.

Wimsatt and Lewis (1948) thoroughly discussed the subject of double mitral orifice under the designation of *duplication of the mitral valve*. These authors described a double orifice of the mitral valve in a yak calf. In a search of the literature, they found 14 cases of the condition in man. In 9 of the 14 cases, one of the two mitral ostia was smaller than the other and, with 2 exceptions, the smaller opening lay ventral to the larger opening. In 5 cases the two ostia were approximately the same size. Wimsatt and Lewis, however, were unable to reach an agreement as to the developmental basis for the double mitral orifice in the heart of the yak. Wimsatt held that the accessory mitral orifice was not an opening in one of the mitral leaflets but resulted from bisection of the mitral orifice into two distinct orifices because of an abnormal fusion between the anlagen of the medial and lateral mitral leaflets. He assumed that an abnormal bridge of tissue had passed across the left atrioventricular orifice and that this bridge had joined the lateral and medial mitral valvular primordia (See Figure II-17). Lewis, however, set the basis for the abnormality at an earlier stage in development of the heart (portrayed in Figure II-17c). He believed that the accessory opening represented persistence of part of the embryonic common atrioventricular canal and incomplete fusion of the endocardial cushions. Shaner (1949) stated that "the explanation favored by Lewis seems more probable, but that of Hartmann (1937) and Wimsatt is not impossible." The true developmental basis for double mitral orifice, therefore, is still controversial.

The occurrence of double orifice of the tricuspid valve is even less frequent than that of double mitral orifice (Wimsatt and Lewis). It is probable, however, that minor degrees of this condition are not uncommon in the tricuspid valve. In otherwise normal hearts the author has, on a number of occasions, seen small openings in the septal leaflet of the tricuspid valve surrounded by attachments of chordae tendineae. He has encountered 2 cases of double orifice of the tricuspid valve associated with papillary muscles related to the accessory orifice (Figure VI-93).

Double orifice of the mitral valve may be associated with persistent common atrioventricular canal (reviewed by Wakai and Edwards, 1958). Double orifice of the mitral valve has been reported as an incidental finding in adults (Schaft and Lisa, 1950, Bowman and Forry, 1953; Prior, 1953, Tremblay and Simard, 1955).

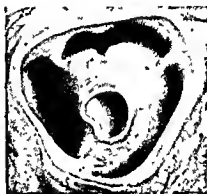


Figure VI-94. Isolated pulmonary stenosis with patent foramen ovale in a man aged 26 years who died of cerebral abscess. The pulmonary trunk has been cut across and the pulmonary valve is viewed from above. The valve is represented by a cone-shaped structure projecting superiorly into the pulmonary trunk. Three raphe radiate from the central part of the cone to the wall of the pulmonary trunk. The opening in the pulmonary valve is considerably narrower than the caliber of the pulmonary trunk which is of normal width. (From Parker, R. L., 1948. Reproduced by permission of the author and the W. B. Saunders Company.)

PULMONARY STENOSIS WITH INTACT VENTRICULAR SEPTUM

Pathologic Anatomy

In pulmonary stenosis, with intact ventric-

ular septum, the obstruction usually lies at the pulmonary valve. Much less commonly

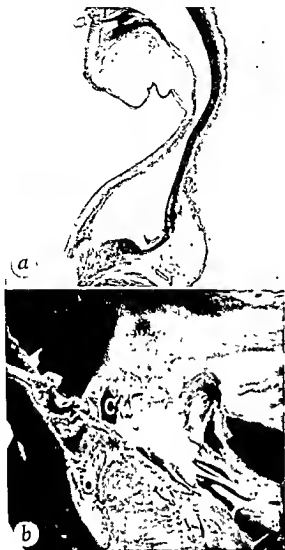


Figure VI-95. *a.* Photomicrograph of pulmonary valve in pulmonary valvular stenosis. From a man 22 years old whose heart is illustrated in Figure VI-96*b*. The free end of the valve shows fibrous thickening, probably in response to the traumatic influence of blood flowing through the stenotic orifice (Elastic tissue stain, X5.) *b.* Tricuspid valve in a case of pulmonary valvular stenosis with intact ventricular septum from a man 23 years old. The valve leaflet shows fibrosis. Evidence of incompetence of the valve is seen in the presence of jet lesions on the right atrial wall just anterior to the right atrial ostium of the coronary sinus (C.).

tricular septum intact variously called *isolated, pure, simple* or *dome-shaped pulmonary stenosis*, the pulmonary valve shows characteristic changes (Figure VI-94). The valve is represented by a dome-shaped or conical fibrous funnel which projects superiorly into the pulmonary trunk. The summit of the dome has a narrow opening, rarely more than several millimeters in diameter. This is the only opening at the level of the pulmonary valve. Probably no other type of congenital cardiac malformation presents greater uniformity in appearance of different specimens. When viewed from above, the dome reveals 3 *raphes* which extend from the central perforation in it, along its superior surface to the wall of the pulmonary trunk (Blackford and Parker, 1941; Currens *et al.*, 1945; Auerbach and Harper, 1947). These raphes probably represent locations at which division of 1 cusp from another should have occurred. In a rare case the valve has 4 instead of 3 raphes. The pulmonary valvular tissue may show fibrous thickening, especially at the border of the orifice (Figure VI-95*a*). Focal calcification of mild degree may be seen, but usually only in older patients.

The *tricuspid valve* is often described as thickened, with fibrous tissue along the line of closure and at the points of attachment of the chordae tendineae (Auerbach and Harper, 1947). Focal calcification occurs rarely. The changes result from the great stress placed upon the tricuspid valve during systole, since systolic pressure of the right ventricle in isolated pulmonary stenosis is far greater than under normal conditions. Changes in the tricuspid valve may, therefore, be regarded as a natural reaction to the excessive physical stresses placed on this valve. These secondary changes may cause the tricuspid valve to become incompetent (Figure VI-95*b*).

The *ventricular septum* is normally formed. The *right ventricle*, however, shows distinctive severe hypertrophy of the concentric type, the right ventricular chamber appearing to be smaller than normal. This feature is particularly noticeable in the subpulmonary region, where the outlet of the right ventricle may be but a few millimeters in diameter (Figure VI-96). It is still unsettled whether the narrow condition of this part of the right ventricle is congenital or acquired. The author believes that it is acquired as

the valve is normal, the obstruction residing in the outflow tract of the right ventricle. The latter condition has been called "right ventricular infundibular stenosis" or *stenosis of ostium infundibuli*. Since these two anatomic entities cause similar clinical problems, they will be discussed together.

In pulmonary valvular stenosis with ven-

a result of the hypertrophy caused by the severe degree of pulmonary stenosis. In Wood's case (1942) the right ventricle was relatively small but the left ventricle was greatly enlarged, probably as a result of a large right-to-left shunt across an atrial septal defect. Some hearts show an anatomically closed *atrial septum*, others a patent foramen ovale (Figure VI-97). Selzer and associates (1949) found 29 cases of isolated pulmonary stenosis with patent foramen ovale and 23 with closed foramen ovale. The patency is usually of the valvular-competent type, although a true atrial septal defect may exist.

The narrow opening in the valve is in striking contrast to the diameter of the *pulmonary trunk*. The latter is often significantly dilated (Greene *et al.*, 1949), a condition called "poststenotic dilatation." The pulmonary trunk or one of its branches near the bifurcation may show a raised area which microscopically is seen to be composed of fibrous tissue. Such a lesion is similar to the regurgitant pockets in the endocardium in cases of valvular insufficiency and in the intima of the left pulmonary artery opposite the mouth of a patent ductus arteriosus. We believe that such "jet lesions" indicate that an abnormal current had existed during life.

Few observations on the *bronchial arteries* have been reported in instances of isolated pul-

monary stenosis. These vessels have been described as dilated in cases of isolated pulmonary stenosis with patent foramen ovale (Vandam *et al.*, 1947, in a girl aged 17 years; Selzer *et al.*, 1949, in a man of 39). They have also been observed by the author in a man of 26 (Figure VI-98). Dilated bronchial arteries have apparently not been described in cases of pulmonary stenosis with closed atrial septum. Functional benefit is derived from a collateral supply to the lungs in cases with open foramen ovale in which venous blood enters the arterial side of the circulation, but the mechanism for development of such collaterals is not evident. The stimulus for enlargement of the collateral vessels may be provided by the low pulmonary blood pressure that exists in this condition.

Infundibular stenosis of the right ventricle is usually associated with a ventricular septal defect (Lev and Strauss, 1942), less commonly with an intact ventricular septum. (See page 320.) The stenosis, although usually not as severe as in cases of valvular stenosis, is localized in the lowermost portion of the outflow tract of the right ventricle. Above the stenosed portion, the *right ventricular wall* is thin, while below it the wall is greatly hypertrophied. The pulmonary valve is normal. Cases of infundibular stenosis with intact ventricular septum have been described (Carr and

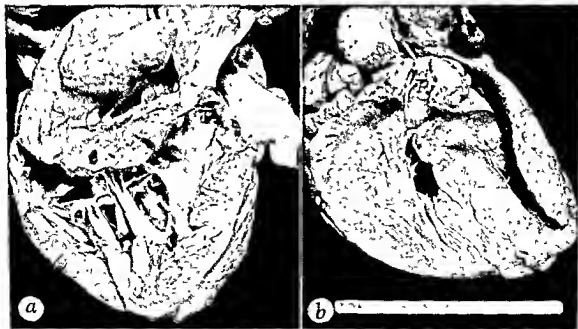
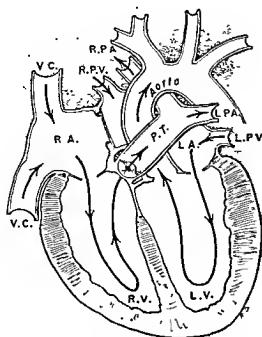
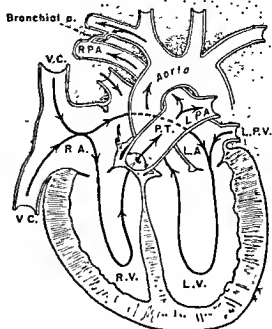


Figure VI-96. Right ventricle and infundibular tract in pulmonary valvular stenosis with intact ventricular septum. *a.* From a woman 60 years old without stenosis of the infundibular tract (*P.* indicates pulmonary valve). *b.* From a man 22 years old. Beneath the pulmonary valve (*P.*) the severe localized hypertrophy of the right ventricular wall causes infundibular stenosis. During life this secondary obstruction was identified by functional studies made at the time of operation. (From Kirklin *et al.*, 1953. Reproduced with permission of Grune & Stratton, Inc.)



a



b

Figure VI-97. Intracardiac circulation in pulmonary stenosis with intact ventricular septum. *a*. The atrial septum is intact. The route of the blood is normal. *b*. Because of the presence of an interatrial communication, a right-to-left shunt at atrial level is possible. This occurrence is responsible for desaturation of arterial blood.

Levi, 1939, Coelho and de Oliveira, 1951, Theilen and January, 1951). Infundibular stenosis may be a primary condition or may be secondary to pulmonary valvular stenosis. In the former, the obstruction is more localized than in the latter.

Associated Conditions

Except for the common association of an interatrial communication, pulmonary stenosis with intact ventricular septum does not often coexist with other cardiovascular malformations. Patent ductus arteriosus has been described in isolated cases (Gordon and Perla, 1931, Taylor and DuShane, 1950, Deuchar and Zak, 1952). Heiner and Nadas (1958) described 6 cases of pulmonary valvular stenosis and patent ductus arteriosus. Each patient also had some noncardiac anomalies, such as mental retardation, microcephaly, cataracts, nystagmus, retinal degeneration, strabismus and deaf-mutism.

A right aortic arch is uncommon, having been observed once in 71 cases by Campbell (1954). Other conditions that may be associated include aortic valvular disease; bicuspid aortic valve; congenital aortic and pulmonary valvular stenosis (Horlick and Merriman, 1957); calcific aortic stenosis (in a 65-year-old man, reported by Carr

and Levi, 1939); subaortic stenosis (in a 19-year-old boy with pulmonary valvular stenosis and intact ventricular septum, reported by Beard *et al*, 1957). Stenosis of a branch of the pulmonary trunk may be associated with pulmonary valvular stenosis, as in a clinical case of Vermillion and associates (1958) that was studied by cardiac catheterization and angiocardiology. Rarely, pulmonary valvular stenosis is associated with a *small ventricular septal defect*. If the defect is small, it is not the dominant lesion (McCord *et al*, 1957) and the essential functional derangements are those of intact ventricular septum with pulmonary stenosis (McGoon and Kirklin, 1958). The one difference is that a right-to-left shunt may occur through the small defect if the right ventricular pressure exceeds that of the left.

Incidence and Sex Distribution

Campbell (1954) found 41 instances (6 per cent) of pulmonary stenosis among 670 patients with cyanotic congenital heart disease and 72 instances (16 per cent) of pulmonary stenosis among 460 acyanotic patients. Thus, pulmonary stenosis is found in 10 per cent of all patients (113 of 1130) with congenital cardiac disease. The sex distribution is about equal.

Functional and Clinical Features

The essential functional disturbance is *obstruction to emptying of the right ventricle*. This results in elevation of right ventricular pressure, the degree of elevation depending upon the severity of the obstruction. The pulmonary arterial pressure is low or normal (Greene *et al.*, 1949, Dow *et al.*, 1950). The right ventricular pressure may equal or exceed the left ventricular pressure (Pollack *et al.*, 1948). Kirklin and associates (1953) have pointed out that, when infundibular stenosis alone is present, this lesion may readily be identified by evidence of low pressure in the subpulmonary region of the right ventricle. When, however, infundibular stenosis is associated with valvular obstruction, the infundibular stenosis may not be apparent if the pulmonary valvular stenosis causes more severe obstruction.

The clinical features in pulmonary stenosis have been reviewed (Engle and Taussig, 1950, Campbell, 1954, Dimond and Lin, 1954, Gibson *et al.*, 1954). Selzer and associates (1949) have emphasized that the level of saturation of the systemic arterial blood depends primarily on whether a *right-to-left shunt* exists at the atrial level. If the atrial septum is intact, no shunt is possible, and no matter how severe the pulmonary obstruction may be, the systemic arterial blood is fully saturated with oxygen, and central cyanosis does not occur. Among patients having an interatrial communication, a right-to-left shunt is possible but not constant. If a right-to-left shunt occurs, it varies in degree from patent to patient; it may also vary in degree with the respiratory cycle and may be intensified by exercise (Campbell, 1954). Cyanosis may be absent, apparent, or severe. The basis for the right-to-left shunt probably resides in the great thickness of the right ventricle which may exceed that of the left ventricle. The distending pressure necessary to fill the right ventricle may then be greater than that needed to fill the left ventricle. These circumstances and the presence of an interatrial communication would lead to a right-to-left shunt.

In a specimen submitted to the author by Dr. Lall C. Montgomery, the right ventricular mural endocardium of an infant with pulmonary valvular stenosis was greatly thickened. This patient had a significant right-to-left shunt, apparently because of restriction in diastolic excursion of the right ventricle as a result of the endocardial thickening.

If during cardiac catheterization the catheter

is in a small pulmonary orifice, the obstruction so caused may be associated with an intensified *right-to-left shunt* (Episcopo *et al.*, 1952). Among cyanotic patients, clubbing and polycythemia may be present but squatting is uncommon. Many patients exhibit normal tolerance for exercise for many years, especially when they are acyanotic. The area of the pulmonary stenosis is associated with a *murmur and thrill*. The second cardiac sound in the pulmonary area is single and not accentuated. *Electrocardiographic changes* in pulmonary stenosis (Joly *et al.*, 1952; Campbell and Reynolds, 1954; Landtman, 1954; Emslie-Smith *et al.*, 1956) seem to depend on the degree of elevation of right ventricular pressure. With great elevations of pressure, the pattern tends to show right ventricular hypertrophy, in other cases, right bundle-branch block. Evidence of right atrial enlargement is common.

Roentgenographic studies characteristically show dilatation of the pulmonary arterial segment, a manifestation of poststenotic dilatation. The pulmonary fields may be normal or show diminished markings. The shadow of the heart itself may be normal in the postero-anterior projection. When enlargement occurs, it tends to

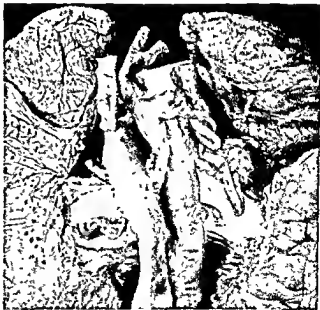


Figure VI-93. Dilated bronchial arteries in the case of isolated pulmonary stenosis, illustrated in Figure VI-94. The mediastinal structures and the adjacent portions of the lungs are viewed dorsally. The right bronchial artery arises from the aorta, ascends, curves behind the esophagus, and then proceeds inferiorly in a tortuous manner to the hilus of the right lung. The left bronchial artery passes horizontally from the aorta to the hilus of the left lung. It curves at a level corresponding to the inferior aspect of the left bronchus.

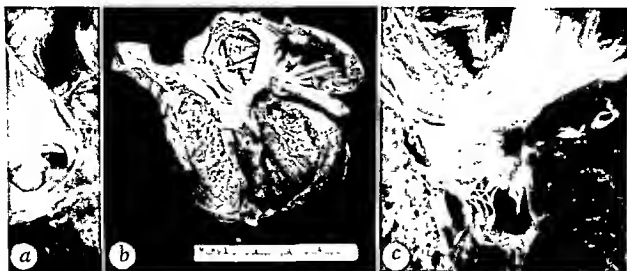


Figure VI-89. Pulmonary atresia with small right ventricle in a male infant 4 months of age. *a*, Pulmonary valve viewed from above. The orifice is closed by a fibrous membrane from the center of which three raphe radiate to the wall of the pulmonary trunk. *b*, Right side of heart. The diminutive size of the right ventricular cavity is in profound contrast to the great thickness of its wall. *c*, The tricuspid valve, though small, appears normally formed.

be toward the right and probably is a sign of right atrial dilatation. Of special roentgenographic interest are cases of pulmonary stenosis with left-to-right shunts (Deuchar and Zak, 1952; Moffitt *et al.*, 1954; Bowers *et al.*, 1956) caused either by patent ductus arteriosus or anomalous connection of pulmonary veins with the right atrium. At other times, there is simply an atrial septal defect and the pulmonary stenosis is either mild or moderate. The features of pulmonary stenosis are evident and these are associated with the exceptional feature of roentgenographic evidence of increased pulmonary flow.

Differential Diagnosis

Little difficulty in diagnosis is encountered in cyanotic or acyanotic patients although in earlier days some of the latter cases were called "examples of small ventricular septal defect" on the basis of the basal murmur and thrill. At times it may be difficult to distinguish the disease from the anatomic tetralogy of Fallot with severe pulmonary stenosis. Identification of different pressures in the two ventricles and occurrence of the right-to-left shunt only at the atrial level usually serve to establish the correct diagnosis. In severely cyanotic infants, the distinction from pulmonary atresia with intact ventricular septum may be difficult unless dye-dilution studies and angiocardigraphy demonstrate a pathway of flow into the pulmonary trunk.

Complications and Prognosis

The major complications are congestive cardiac failure, bacterial endocarditis, cerebral abscess, and hypoxia. *Cardiac failure* is the most common. *Bacterial endocarditis* may begin at any one of the sites of great stress: (1) tricuspid valve (McPhedran, 1924), (2) pulmonary valve (Tuley and Moore, 1917), (3) bifurcation of the pulmonary trunk (at which site the jet stream of blood strikes when valvular stenosis is present), and (4) wall of the right ventricular infundibular chamber above localized infundibular stenosis (Leitman, 1928). *Cerebral abscess* is seen only among patients having interatrial communication and is explained as a complication of a right-to-left shunt, as in patients with other anatomic malformations in whom a right-to-left shunt occurs (Parker, 1948; Selzer *et al.*, 1949). *Hypoxia*, a relatively uncommon cause of death, is probably seen only in infants with severe stenosis (Johnson and Johnson, 1952). In such cases an element of cardiac failure is probably also present. Death may occur during infancy, particularly if the stenosis is severe, but most patients survive to adult life. In the series of Abbott and associates (1923) the average age at death was 21 years. The patient of White and associates (1950) lived to the age of 75 years.

Surgical Correction

Pulmonary valvotomy is the accepted proce-

cedure for pulmonary valvular stenosis (Brock, 1948, Sellors, 1948, Brock and Campbell, 1950). When secondary infundibular stenosis occurs, residual obstruction may be apparent after this procedure, however (Kirklin *et al.*, 1953). Infundibular resection may relieve this compli-

cating factor (McGoon and Kirklin, 1958). Engle and associates (1958) have indicated that spontaneous regression of infundibular stenosis may occur in some patients simply after relief of the pulmonary valvular stenosis

PULMONARY ATRESIA WITH INTACT VENTRICULAR SEPTUM

This condition must be distinguished from pulmonary stenosis with intact ventricular septum. Patients with pulmonary stenosis usually live to adolescence or adult life, whereas patients with pulmonary atresia and intact ventricular septum rarely, if ever, live beyond infancy. In pulmonary atresia the pulmonary valve is closed by a fibrous diaphragm. When viewed from above, the diaphragm appears to be formed by fusion of 3 cusps. Radiating from the center of the diaphragm are 3 equidistant ridges (Figure VI-99a). These extend to the wall of the pulmonary trunk or end at the junction of the fused cusps with the arterial wall. The 3 ridges are similar in appearance to the 3 ridges or raphe usually seen in the superior aspect of the fused cusps in cases of dome-shaped pulmonary stenosis. The lack of an

opening within the fibrous membrane representing the fused pulmonary cusps distinguishes isolated pulmonary atresia from isolated pulmonary stenosis. The function of the heart and the secondary pathologic features depend on whether there is an opening, however small, in the pulmonary valve.

In all cases of pulmonary atresia with intact ventricular septum, there is no normal outlet for blood from the right side of the heart. An interatrial communication exists which usually takes the form of a valvular-competent patent foramen ovale. Rarely a true atrial septal defect is present. The left atrium and left ventricle are somewhat enlarged as the aorta arises normally from the left ventricle. The aorta is unusually wide. A patent ductus arteriosus provides communication between the aorta and the pulmonary



Figure VI-100. Pulmonary valvular atresia with intact ventricular septum, incompetent tricuspid valve and normal-sized right ventricle in a female infant 7 weeks old. *a.* The great vessels are correctly interrelated. The pulmonary trunk is narrower than normal. *b.* Interior of right side of heart. In contrast to the right ventricle of the type illustrated in Figure VI-99, the chamber here is of normal size. The right atrium is dilated. The difference in appearance of the right ventricle in cases of pulmonary valvular atresia appears to depend on whether the tricuspid valve is incompetent. In this instance, the valve was regarded as incompetent.

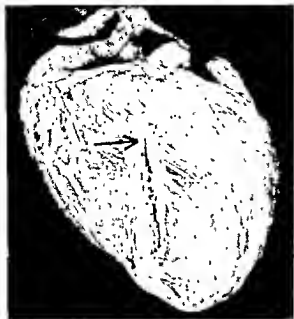


Figure VI-101. Anterior view of the heart in atresia of pulmonary valve with intact ventricular septum and small right ventricle. From a male infant 8 days of age. Near the intraventricular sulcus and to the right of the anterior descending coronary artery, an anomalous vessel emanates from the right ventricle (point of arrow.) The vessel communicated with the branches of the anterior descending coronary artery and originated by fusion of sinusoids of the right ventricular chamber.

arterial system. The latter may be of normal caliber, although in some instances the pulmonary trunk is narrower than normal.

Greenwood (1953) divided pulmonary atresia with intact ventricular septum into 2 groups, depending on the size of the right ventricle. The first group is characterized by a small right ventricular chamber while in the second group, the right ventricular chamber is of normal size or somewhat enlarged. It is important to separate these 2 categories since, at present, surgical relief of the pulmonary obstruction is possible only in the second group. In the first group, the right ventricular chamber is minute but the right ventricular wall is greatly hypertrophied, measuring up to 2 cm. in thickness in infants (Figure VI-99b). A thrombus may fill the cavity (Glaboff *et al.*, 1950). The tricuspid valve, although diminutive, appears properly formed. Here we have the combination of pulmonary atresia, a closed ventricular septum and a normally functioning tricuspid valve apparently as the underlying factors in the enormous right ventricular hypertrophy. It appears that some blood may enter the ven-

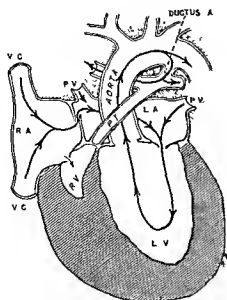
tricle during diastole, but cannot escape as long as the tricuspid valve remains competent. This means that during systolic contraction the right ventricle contracts against a noncompressible substance and therefore becomes markedly hypertrophic. This assumption seems to be supported by cases of pulmonary atresia with a closed ventricular septum and an atretic tricuspid valve (see Tricuspid Atresia, Type Ia, page 377). In the latter condition, in which no blood can enter the right ventricle, the chamber is tiny and its wall is so small as to be easily overlooked at necropsy (Figure VI-79a). Unless sections are taken from appropriate locations and studied microscopically to determine the presence of a cardiac chamber, one may at times be unable to demonstrate the right ventricle (Elster, 1930). Even when the right ventricle is of normal size or enlarged, the wall is hypertrophied (Figure VI-100). Hearts with small right ventricular chamber often have an anomalous vessel emanating from the right ventricular chamber (Figure VI-101). It is formed by coalescence of sinusoids in the myocardium of the right ventricle. The single vessel emerges into the epicardium and communicates with the branches of the normal coronary arteries. In discussing the pathogenesis of this anomalous coronary vessel, Williams and associates (1951) have indicated that, in the presence of an absolute obstruction at the pulmonary valve and a functioning tricuspid valve, elevation of right ventricular pressure would force open widely those myocardial sinusoids which normally are present but narrow. By fusion, these channels would develop into the anomalous coronary vessel mentioned.

Incidence and Sex Distribution

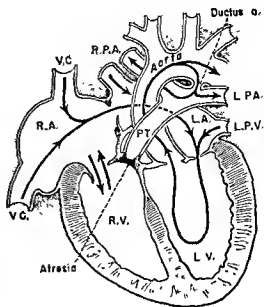
Pulmonary atresia with intact ventricular septum is uncommon. Among 83 cases of pulmonary stenosis and atresia of all varieties which Abbott and associates studied in 1923, only 6 were cases of pulmonary atresia with intact ventricular septum. In the Mayo Clinic pathologic collection of more than 550 hearts, there are 17 examples of this condition. Among 16 cases in which the sex was known, 10 were from males and 6 from females.

Functional and Clinical Features

As in tricuspid atresia, all the blood which enters the right atrium through the venae cavae and the coronary sinus is directed into the left atrium (Figure VI-102). Here it is met by oxygenated blood entering the left atrium by way



a



b

Figure VI-102 Intracardiac circulation in pulmonary valvular atresia and intact ventricular septum. *a.* The right ventricular chamber is small. The tricuspid valve was regarded as competent *b.* The right ventricular chamber is of normal size or enlarged. The tricuspid valve was believed to have been incompetent

of the pulmonary veins. The left atrium is thus, functionally, a single atrium, and communicates normally with the left ventricle through the mitral valve. The aorta receives all the blood which leaves the heart. The ductus arteriosus is usually open and through it the lungs receive the major part of their blood. The diameter of the patent

ductus arteriosus is probably always inadequate to carry an optimal amount of blood to the lungs. *Cyanosis*, often of intense degree, is the most striking clinical feature. It is usually noted at birth or shortly thereafter. The electrocardiogram usually shows evidence of right ventricular hypertrophy (Novelo *et al.*, 1951). The roentgeno-



Figure VI-103 Roentgenograms of the thorax in two cases of pulmonary valvular atresia with intact ventricular septum. *a.* From an infant with a small right ventricular chamber. *b.* From an infant with an enlarged ventricular chamber whose heart was illustrated in Figure VI-100. The increase in transverse diameter of the heart is characteristic of most cases of normal-sized or enlarged right ventricular chamber. Dilatation of the right atrium contributes to part of the enlargement.

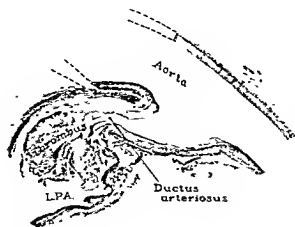


Figure VI-104. Photomicrograph of the great vessels in a case of pulmonary valvular atresia with intact ventricular septum in an infant 7 weeks old. The pulmonary end of the ductus arteriosus is obliterated by a thrombus. It is presumed that clinically the accentuation of cyanosis was related to this complication. (L.P.A. indicates left pulmonary artery)

graphic appearance of the thorax depends on the size of the right ventricle, if the chamber is small, the cardiac shadow is not enlarged, if the right ventricle is of normal size or enlarged, the cardiac shadow is enlarged with significant enlargement to the right (Figure VI-103).

Complications and Prognosis

The major complication is narrowing of the ductus arteriosus, the main channel by which

blood is carried to the lungs. This narrowing usually proceeds along normal lines and almost uniformly accounts for early death. Rarely thrombosis of the ductus arteriosus may be the basis for closure (Figure VI-104). Leo (1886) reported this condition in a girl who died at the age of 8 months. He stated that 14 other cases had been reported up to that time and that, with the exception of Hare's patient, who died at the age of 9 months, all patients had died in the neonatal period. In Abbott's series (1923) the longest survival was 16 weeks. The oldest patient observed by Edwards died at 11 months. The longest survival, as far as I am aware, was that of a 14-year-old girl (Allanby *et al.*, 1950).

Surgical Correction

The anticipated results from pulmonary valvotomy depend on the size of the right ventricular chamber. Among patients with a small right ventricular chamber, it is doubtful whether relief of the pulmonary valvular obstruction would accomplish much. The small caliber of the tricuspid valve and the small capacity, either alone or together, would produce significant resistance to right ventricular filling. If the right ventricle is normal or enlarged, relief of the pulmonary valvular obstruction might be helpful. Since the basis for a normal-sized or enlarged right ventricle is tricuspid insufficiency, the latter may present a residual significant problem even after the primary condition was corrected.

AORTIC ATRESIA WITH INTACT VENTRICULAR SEPTUM; COEXISTENT AORTIC AND MITRAL ATRESIA

Pathologic Anatomy

In aortic atresia (Figure VI-105a) and in coexistent aortic and mitral atresia (Figure VI-105b), with intact ventricular septum, the appearances of the aortic valve are similar. The orifice is closed by a fibrous diaphragm (Canton, 1849; Figure VI-106a) similar in appearance to the atretic pulmonary valve in cases of pulmonary atresia. The coronary ostia lie superior to the membrane. In each condition the ventricular septum is intact. Except for the appearance of the left ventricle and mitral valve, the two conditions show the same secondary phenomena.

In coexistent aortic and mitral atresia the left ventricular chamber is tiny (Walker and

Klinck, 1942), and its wall is so thin as to escape detection at times, unless histologic sections taken from appropriate locations are studied (Figure VI-105b). The left ventricle in this condition is similar to the right ventricle in cases of coexistent pulmonary and tricuspid atresia; the latter are designated in this chapter as tricuspid atresia, Type 1a. Some cases reported as examples of aortic and mitral atresia with a single ventricle are probably examples of this malformation. Inasmuch as the left ventricle is a chamber without any function, the malformation has been given the name *cor pseudotriloculare* (Dolgopol, 1934).

In isolated aortic atresia the left ventric-

ular cavity is small but its wall is greatly thickened (Figures VI-105a and VI-106b; Wenner, 1909, Case 7). This feature is similar to the great thickness of the right ventricular wall when pulmonary atresia is associated with a closed ventricular septum and a patent tricuspid orifice. The increased thickness of the wall apparently is caused by contraction of the ventricle against blood caught in the chamber as a result of the aortic atresia and a functioning mitral valve. In cases of aortic atresia or of coexistent aortic and mitral atresia, the left atrium may be normal in size, or smaller or larger than normal. Since there is no normal outlet from the left side of the heart, an unusual route must be present for exit of blood from the left atrium. The situation with respect to flow of blood from the left atrium is identical to that in cases in which mitral atresia is the basic malformation. The thebesian veins in the atrial septum may be wider than normal and so carry blood from the left atrium into the right. These outlets, no matter how much wider than normal they may be, are never sufficient to carry an adequate amount of blood.

If life after birth is maintained, the interatrial communication is larger (Figure VI-106b and c). At times this takes the form of an atrial septal defect, represented by a short valve of the foramen ovale, as in the second case of Willer and Beck (1932). More commonly the foramen ovale is patent for another reason. Evidently as a result of the great pressure which is built up in the left atrium, the anterior aspect of the valve of the foramen ovale is forced through the foramen ovale into the right atrium, to create an atrial septal defect. Though the opening is often described merely as a "patent foramen ovale," it should be recognized as a peculiar form of patency. It is similar to the usual patent foramen in cases of mitral atresia.

The patient of Bellet and Gouley (1932), with isolated aortic atresia, died 12 hours after birth and showed a *prematurely closed foramen ovale*. In McIntosh's (1926) case of mitral atresia and premature closure of the foramen ovale, an anomalous channel connected the left atrium and the superior vena cava. Through this channel,

blood could leave the left atrium and eventually reach the right atrium (see sections on Mitral Atresia, page 386, and Malformations of the Great Veins (page 481). Ruge (1905) found that the foramen ovale was closed in 5 of 50 reported cases of congenital aortic atresia. He stated that while fetal life is possible in such cases, postnatal life is not. Unless an unusual vascular connection exists, such as that suggested by Bellet and Gouley, the statement of Ruge is entirely justified.

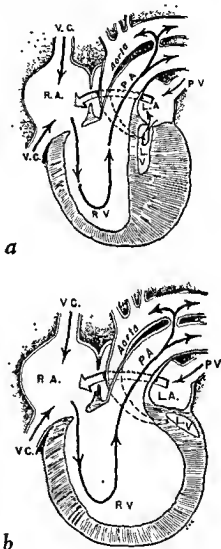


Figure VI-105. a. The intracardiac circulation in aortic atresia. The left ventricle, although having a small chamber, has a greatly thickened wall (From Edwards, J. E.: *Postgrad. Med.*, 3:327-341, 1948. Reproduced by permission of *Postgraduate Medicine*.) b. The intracardiac circulation in coexistent aortic and mitral atresia. The left ventricular chamber is diminutive and is hidden in the wall of the single functioning right ventricular chamber.

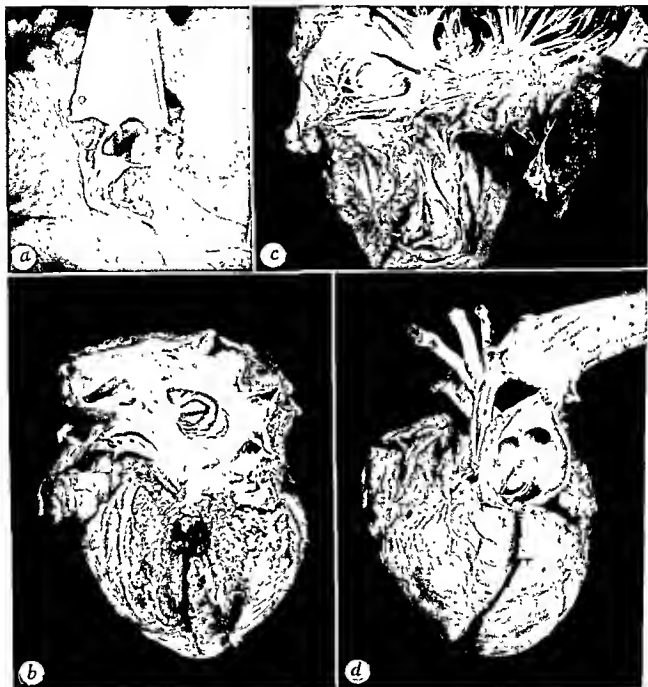


Figure VI-106. Aortic atresia in a female infant 4 months old. (Reported by DuShane, J. W.: *M. Clin. North America*, 32 879-894, 1948, Case 2.) *a* The ascending aorta has been opened, and the aortic valve is seen from above. A membrane closes the valve orifice. Three raphe radiate from the center of the diaphragm to the aortic wall. *b* The left ventricular wall is greatly thickened. The chamber is small. The mitral valve is normally formed, but small. Prominent thebesian veins are seen in the atrial septum. *c* The right side of the heart. The right atrium is greatly dilated. A probe lies in the small patent foramen ovale. The right ventricular chamber is dilated and its wall is hypertrophied. *d* The great vessels and the exterior of the heart. The pulmonary trunk is widely patent and is correctly related to the hypoplastic ascending aorta. A patent ductus arteriosus connects the pulmonary arterial system with the aorta. (From DuShane, 1948.

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The right atrial chamber is dilated (Figure VI-106c), and the right ventricle dilated and hypertrophied. The pulmonary trunk is greatly dilated but its relationship to the aorta is normal. While the aortic arch is of normal size, the ascending aorta is considerably narrower than normal. It is often described as "hypoplastic" (Figure VI-106d), and may be only several millimeters in diameter. The ductus arteriosus is patent and represents the only channel by which the systemic circulation derives its blood, the source being the pulmonary arterial system.

Aortic atresia is often accompanied by great thickening with elastic tissue of the left atrial and left ventricular mural endocardium and myocardial scarring (Wiglesworth, 1936; Rossman, 1942). In coexistent aortic and mitral atresia, the left atrial endocardium is similarly thickened. Some have explained this change as representing the end-result of fetal endocarditis which also was responsible for the valvular atresias (von Zalka, 1924). Others have thought that the fibrous thickening of the mural endocardium is merely the result of the mechanical stresses incident to the obstruction at valve level (Stiasny, 1901; Loeser, 1915). The latter interpretation seems correct. It must be pointed out that the myocardial scarring usually lies immediately beneath the thickened endocardium (von Zalka). The scars of the myocardium are probably continuous with the thickened endocardial connective tissue. Von Zalka observed that in hearts with pulmonary atresia the right ventricular mural endocardium and underlying myocardium were scarred, and that similarly in aortic atresia the left ventricular endocardium and myocardium were scarred. He felt that these observations supported the concept that the basis for the valvular atresia was inflammatory. We believe, however, that these changes are better explained on a mechanical basis. Cellular infiltration is rarely associated with the endocardial thickening and myocardial scarring (Isaacson *et al.*, 1946). In occasional cases there are many wide blood-containing channels in the myocardium of the left ventricle and atrium (von Zalka, 1924; Bellet and Gouley, 1932). In their case, Bellet and Gouley could trace continuity of these sinuses with the smaller coronary arteries on one hand, and with the cardiac chambers on the other. Such abnormal coronary blood vessels are similar to those seen in pulmonary atresia with intact ventricular septum and a competent tricuspid valve.

At necropsy the lungs usually exhibit edema. The arterial vessels show medial hypertrophy, but because of the young ages of the patients it is

impossible to distinguish these features from the normal, however significant the changes may be.

Incidence and Sex Distribution

The incidence of aortic atresia is relatively low. Abbott's (1936) series of 1000 hearts included 12 instances of aortic atresia. This presumably included cases of isolated aortic atresia and those of coexistent aortic atresia and mitral atresia. The incidence for some reason is much higher in the collection of the Mayo Clinic. Among more than 550 specimens with major cardiovascular malformations, 10 had coexistent aortic and mitral atresia and 20, aortic atresia with intact ventricular septums. Many of these specimens were submitted from outside sources, probably because of their relative rarity.

There is a decided tendency for aortic atresia to occur in the male. Friedman and associates (1951) reported that among 27 cases of aortic atresia and coexistent aortic and mitral atresia in which the sex was known, 18 were in males. In the collection of the Mayo Clinic, among 8 cases of coexistent aortic and mitral atresia in which the sex was known, 6 were in males and 2 in females. In the same series, among 16 cases of aortic atresia with intact ventricular septum in which the sex was known, 14 were in males and 2 in females. Brekke (1953) reported aortic atresia in 2 members of the same family.

Functional and Clinical Features

In both aortic atresia with intact ventricular septum and in coexistent aortic and mitral atresia, the circulation is essentially the same in that blood from the left side of the heart has no outlet (Figure VI-105). Blood which returns to the left atrium from the pulmonary veins meets an obstruction and is carried through a narrow communication to the right atrium, usually through an interatrial communication. This rarely occurs through anomalous venous connections. The right atrium receives, in addition, all the blood returning normally through the systemic veins. The mixture of blood in the right atrium enters the large right ventricle which is the only effective propelling ventricle. From the pulmonary arterial system, blood is directed both into the lungs and through the ductus arteriosus into the aorta. It is recognized that the aortic arch and the coronary arteries receive blood which flows in the reverse direction of the normal. Proximal to the innominate artery, the hypoplastic ascending aorta is, from a functional point of view, simply a common coronary artery.

Two major functional disturbances are present.

One is obstruction to pulmonary venous flow resulting from the abnormally narrow outlet of the left atrium, and at the same time, the right ventricle represents a common functioning ventricle for both the pulmonary arterial and systemic arterial systems. There is then an inverse relationship between pulmonary and systemic flow, and with this follows differences in functional manifestations. When pulmonary flow is increased, desaturation of the systemic arterial blood tends to lessen, but this, at the same time, leads to a greater tendency to pulmonary edema. When the pulmonary blood flow is decreased, pulmonary edema tends to become less, but at the same time, a greater proportion of systemic venous blood is present in the mixture of blood in the right side of the heart, thus producing a greater tendency for cyanosis.

Patients with aortic atresia manifest cyanosis shortly after birth (Taussig, 1945; Friedman *et al.*, 1951). In some cases a precordial murmur, usually systolic, is best heard to the left of the sternum. The roentgenogram gives evidence of marked cardiac enlargement. The electrocardiogram usually indicates right ventricular enlargement; rarely, left ventricular hypertrophy (Soloff, 1949). Lev and Killian (1942) reported isolated aortic atresia in 2 patients who had had first degree atrioventricular block during life and prolonged QRS complexes. Histologic studies were made of the conduction system. In the first patient, who lived 44 hours after birth, the atrioventricular node was normal, the bundle of His was embedded in and partly penetrated by a large mass of scar tissue, and the distal portion of the left branch of the bundle was encased in and partly subdivided by hyalinized connective tissue of the left ventricular mural endocardium. The findings in the second patient were essentially similar.

Complications and Prognosis

Hershheimer (1910) found that many patients die during fetal life. Of those who are born alive, the majority die during the first week of postnatal life. Friedman and associates (1951), reviewing 36 cases, mostly from the literature, found that the oldest patient had lived 4 months.

Of the 36 patients, 24 were dead within the first week after birth. The striking tendency for aortic atresia to be lethal early in life accounts for the frequency of this malformation in reviews of congenital defects occurring in the newborn period, in contrast to the lower incidence when patients of all ages are studied. The major cause of death is pulmonary edema.

Developmental Basis

The developmental basis for aortic atresia is not established. In view of the intact ventricular septum, it is assumed that the valvular malformation is formed relatively late in the period of cardiac development. Some (Farber and Hubbard, 1933; Abbott, 1936) have suggested that the atresia represents the end-stage of fetal endocarditis, but this is not proved. Histologic examination of the myocardium in the cases reported by von Haam and Hartwell (1939) and by Rossman (1942) failed to show any evidence of inflammation. Willer and Beck (1932), in 2 cases of isolated aortic atresia, found attached to the obstructing diaphragm, vascular connective tissue including macrophages containing hemosiderin. Though they claimed that these features were evidence of endocarditis, it is possible that the tissue they described represented an organized thrombus. While it is difficult to prove that the malformation is on an inflammatory basis, it is also difficult to explain it otherwise. Although no stage in cardiac development is characterized by anatomic closure of the aortic valve, for some occult reason a secondary fusion of the developing valve cusps occurs. Evidence supporting the concept that the atresia is not caused by unequal partitioning of the truncus arteriosus is found in (1) an intact ventricular septum and (2) the presence, within the diaphragm that closes the aortic valve, of elements which seem to represent 3 aortic cusps. In an earlier section (page 335), it was seen that unequal partitioning of the truncus results in a defect of the membranous portion of the ventricular septum and, in malformations such as the anatomic tetralogy of Fallot, that it results in a narrow pulmonary valve which is often bicuspid.

BICUSPID AND QUADRICUSPID SEMILUNAR VALVES

Either of the semilunar valves may have a deficiency or an excess in the number of

cusps. The most common of these variations is a bicuspid aortic valve.

Bicuspid Aortic Valve

A bicuspid aortic valve always raises the question whether the abnormality is a congenital malformation or an acquired deformity. For this reason it is pertinent to review the criteria for distinguishing these 2 types of bicuspid aortic valves (reviewed by Kolletsky, 1941a and b). Two types of congenital bicuspid aortic valves are found. In one type the two cusps are of equal size and usually it

is evident that a malformation exists (Figure VI-107a). In the second type, 1 of the 2 cusps is divided by a ridge or a raphe into 2 segments (Figure VI-107b). The ridge lies vertically in the aortic wall of the aortic sinus. It extends into the depths of the sinus and may then extend into the sinusal aspect of the conjoined cusp. The conjoined cusp may be equal in size to the other cusp but, more commonly, the conjoined cusp is the larger.

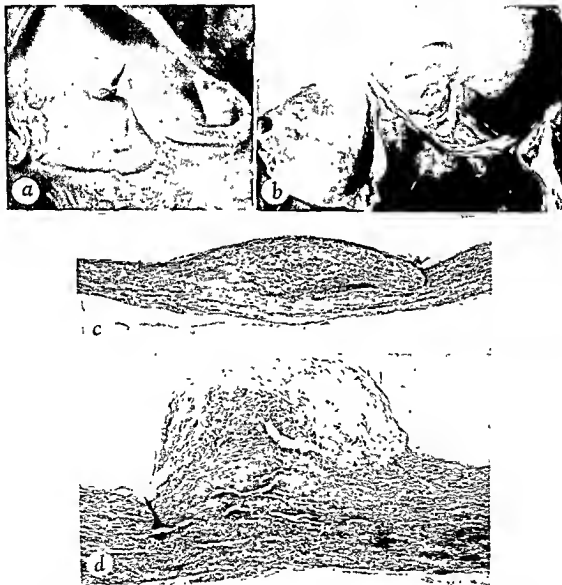


Figure VI-107. *a*. Congenital bicuspid aortic valve in which the two cusps are of about equal size. No raphe is present. *b*. Congenital bicuspid aortic valve. A raphe extends from the aortic wall onto the dorsal one of the two cusps. *c*. Photomicrograph of section across the raphe in congenital bicuspid aortic valve. Aortic media extends uninterruptedly through and forms the raphe. (Verhoeff's elastic tissue stain counterstained with van Gieson's connective tissue stain. X13.) *d*. Photomicrograph of section across the raphe in acquired bicuspid aortic valve. The raphe is composed of collagenous tissue. The aortic media does not extend into it. Contrast with the picture of the congenital raphe illustrated in *c* (Verhoeff's elastic tissue stain counterstained with van Gieson's connective tissue stain. X14.)

Osler (1886) laid down gross criteria for the distinction between acquired and congenital bicuspid aortic valves. Subsequently, however, others (Lewis and Grant, 1923, Bishop and Trubek, 1936; Koletsky, 1941) have pointed out that the gross appearance is unreliable in the differentiation, and that the distinction must be made from the microscopic characteristics of the raphe and of the neighboring aortic wall.

Summary of Microscopic Characteristics. In congenital bicuspid aortic valve the upper part of the raphe is composed exclusively of aortic medial tissue covered by a thin layer of intima (Figure VI-107c). At this level the elastic fibers of the outer media pass without interruption through the ridge and are parallel except in the central portion of the raphe. In the latter location the elastic fibers are whorled and irregular. In the base of the raphe, in the vicinity of the annulus fibrosus, the regular character of the raphe, resembling aortic media, is partly lost. Usually the annulus extends upward and divides the raphe into 2 halves, one superficial and the other deep. Koletsky has compared the shape of the annulus to that of an inverted letter V, the apex of the V being covered by medial tissue of the aorta on each side. Superficial elastic fibers of the raphe may extend down to the attachment of the cusp.

The important point to recall in this arrangement is that part of the aortic media lies superficial to that is, toward the sinus of, the annulus fibrosus. This arrangement is like that seen in the normal aortic wall at the center of the aortic sinus, whereas at the commissure the relationship changes and the *annulus fibrosus lies superficial* to the aortic media. In contrast to the presence of aortic media superficial to the annulus fibrosus at a raphe of congenital type (Figure VI-107c), at a raphe of the acquired type the annulus fibrosus and the aortic media have a normal commissural relationship, the aortic media lying deep to the annulus. The acquired raphe thus contains no medial elements of the aorta (Figure VI-107c) and is composed of the collagenous tissue of the annulus fibrosus overlain by the interadherent elements of the 2 cusps which have become fused. Several strands of elastic tissue may be found in the acquired raphe, but these lack the regularity of the elastic fibers in the congenital raphe.

An acquired bicuspid valve results from inflammatory disease and may show cellular infiltration and vascularization of the raphe, features that

are absent in the raphe of the congenital bicuspid valve.

Koletsky found 18 cases of congenital bicuspid aortic valve among 3300 consecutive necropsies; McGinn (1936), 10 instances among 7500 necropsies; and Leech (1935), 3 instances among 13,115 necropsies. Gross (1937) encountered 28 instances of bicuspid aortic valves in a review of 5000 hearts. None of these occurred in the younger age groups although 932 of the 5000 hearts were from persons less than 10 years of age. The average age of the 28 persons with bicuspid aortic valves was 45 years. He made a special study of 16 of these hearts and concluded that in all of them the aortic valve was bicuspid on an acquired basis. It should be emphasized that in 2 of these hearts the structure of the aortic annulus was like that in congenital bicuspid aortic valve, according to the criteria of Lewis and Grant, Bishop and Trubek, and Koletsky. Gross stated that a bicuspid aortic valve in an adult should not be regarded as a congenital malformation unless other cardiac malformations coexist. This opinion seems unjustified in view of the apparently sound criteria for the distinction of a congenital from an acquired bicuspid aortic valve.

Congenital bicuspid aortic valve may exist as the sole malformation in a given case or it may be associated with other cardiovascular malformations. In Koletsky's (1941a) 18 cases of congenital bicuspid aortic valve, 9 were encountered in infants and children and 9 in adults. Seven of the 9 younger patients had associated anomalies of the heart while 2 of the 9 adults had associated cardiac malformations. Associated cardiovascular malformations in Koletsky's series included transposition of the great vessels, ventricular septal defect, aneurysm of the ventricular septum, persistent ostium primum and, foremost, coarctation of the aorta. The latter malformation was present in 4 of the younger group and in 1 of the adults. In 1 patient, an 8-year-old boy, the congenital bicuspid valve was associated with coarctation of the aorta and an aneurysm of the circle of Willis. Rupture of the latter was the cause of death.

It is estimated that bicuspid aortic valve occurs in 75 per cent of cases of coarctation of the aorta. (Edwards *et al.*, 1948). When associated with coarctation of the aorta, the bicuspid aortic valve may frequently be responsible for aortic valvular insufficiency (Christensen and Hines, 1948, Burchell, 1950). When congenital bicuspid aortic

valve is not associated with other cardiovascular malformations, it usually causes no functional disturbance but constitutes a hazard for the development of *bacterial endocarditis*. Abbott (1925) reported bacterial endocarditis in 18 of 44 cases. Though she accepted a congenital basis for all of the bicuspid valves, in some cases the valvular deformity may have been acquired. Lewis and Grant found that in 8 of 31 cases of subacute bacterial endocarditis the infection started on an aortic valve that was congenitally bicuspid. In discussing these findings, Koletsky (1941a) stated that, as in a previously normal valve, the congenitally bicuspid valve may be complicated by rheumatic inflammation. The acquired deformity of the anomalous valve may make the valve susceptible to a complicating bacterial infection. Hoagland (1950) made a study of anomalous semilunar valves that were observed at necropsy at the Mayo Clinic from 1920 through 1943. They encountered 33 examples of congenital bicuspid aortic valves, in 25 of these, the patients were adults and 5 of the 25 had complicating subacute bacterial endocarditis. Gelfman and Levine (1942) studied 453 cases of congenital cardiovascular malformations, in 181 the patients were 2 years of age or older

at the time of death. Approximately 29 per cent of the patients more than 2 years of age had a bicuspid aortic valve which was regarded as congenital in nature. Eighty per cent of these were not associated with other cardiovascular malformations. Bacterial endocarditis was encountered in 30 of the 181 cases of all cardiac malformations in which the patients were 2 years of age or older. In 7 of the 30 cases of bacterial endocarditis, the aortic valves were congenitally bicuspid.

Bicuspid Pulmonary Valve

While bicuspid pulmonary valves may exist in a pulmonary orifice of normal caliber and may be the sole malformation in a given heart (Figure VI-108a), this condition is usually part of a serious form of cardiac malformation. The most common malformation in association with bicuspid pulmonary valve is the tetralogy of Fallot (Dilg, 1883). Koletsky (1941c) has stated that about one-third of the cases of bicuspid pulmonary valve are associated with the tetralogy of Fallot and, moreover, most hearts with the tetralogy of Fallot have a bicuspid pulmonary valve as



Figure VI-108. *a.* Congenital bicuspid pulmonary valve guarding a nonnal-sized orifice. A raphe extends from the wall of the pulmonary trunk onto the posterior of the two cusps. This was observed incidentally in a heart with no other malformations. *b.* Quadricuspid aortic valve in which three of the cusps are of about equal size. The fourth, toward the right of the illustration, is rudimentary. *c.* Quadricuspid pulmonary valve. One of the cusps is rudimentary.

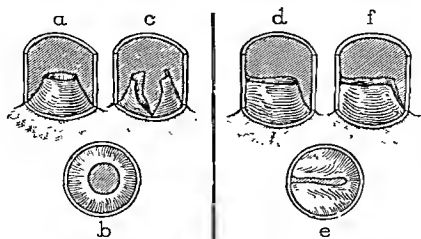


Figure VI-109. Congenital aortic stenosis of simple dome-shaped variety (*a, b, c*) and of unicommisural dome-type (*d, e, f*). *a* and *d* represent lateral views of the valves, *b* and *e* portray the appearance of the valve from above and *c* represents the valve after simulated valvulotomy. The two resulting flaps have no lateral attachment to the aortic wall. In *f* is shown the valve after simulated valvulotomy done opposite the single commissure. This results in two flaps that have no attachment to the lateral wall of the aorta opposite the beginning of the single commissure.

part of the malformation. Other malformations that may have an associated bicuspid pulmonary valve include complete transposition of the great vessels and tricuspid atresia. In these conditions, however, the association of the valvular abnormality does not approach the high incidence seen in the tetralogy of Fallot.

In Koletsky's (1941c) analysis of data in 9 patients with bicuspid pulmonary valve, he found 2 in whom this was the sole malformation. In 3 it was associated with the tetralogy of Fallot, in 1, with a ventricular septal defect, and in 1, with cor triloculare biatriatum and transposition of the great vessels. In 2 of the hearts bicuspid aortic valve was associated. The latter phenomenon, according to Koletsky, is rare, only 4 other such instances having been recorded. In an analysis of the malformations of the semilunar valves observed at the Mayo Clinic from 1920 through 1943, Hoagland found in addition to the 33 cases of bicuspid aortic valve, 7 of bicuspid pulmonary valve, 5 of quadricuspid aortic valves and 15 of quadricuspid pulmonary valves. Of the 7 cases of bicuspid pulmonary valve, 6 were associated with serious forms of congenital cardiac malformations, as follows: tetralogy of Fallot, 3 cases; complete transposition of the great vessels, 2 cases; and ventricular septal defect,

1 case. In the seventh case, the patient, an adult, also had a congenital bicuspid aortic valve.

Quadricuspid Aortic and Pulmonary Valves

Quadricuspid pulmonary valve, as indicated by the studies of Dilg (1883) and Hoagland, is at least 3 times as common as quadricuspid aortic valve. The 4 cusps may be of equal size; 1 of the cusps may be rudimentary and the sizes of the other 3 appear equal and normal (Figure VI-108b); or all of the cusps may vary in size (Figure VI-108c). Usually neither of these semilunar valvular malformations is of functional significance, being discovered unexpectedly at necropsy.

In 1883 Dilg found reports of 24 cases of quadricuspid pulmonary valve and of only 9 instances of quadricuspid aortic valve. He also encountered 2 examples in which the pulmonary valve had 5 cusps and 1 case in which the aortic valve was similarly anomalous. Kissin (1936) reviewed 151 reported and 3 unreported quadricuspid pulmonary valves, and a case which he had observed. In his own case, Kissin judged that the malformation had been responsible for pulmonary valvular incompetence, pulmonary regurgitation was present also in 3 of the reported cases.

AORTIC STENOSIS

Congenitally malformed aortic valves tend to become stenotic. Under some circumstances the stenosis is an integral part of the malformation, under other circumstances, stenosis is acquired. Patients having congenital bicuspid aortic valves have a tendency to acquire calcific aortic stenosis. Often the manifestations of this secondary disease do not become apparent or may not develop until adult life.

Pathologic Anatomy

When aortic stenosis occurs as an integral manifestation of congenital malformation of the aortic valve, the simplest anatomic form bears a close resemblance to the pulmonary valve when it is involved in *congenital dome-shaped stenosis*. Aortic stenosis of this type may be referred to as "simple dome-stenosis" (Figures VI-109a, b and c and VI-110a). A

somewhat more complicated variety of dome-stenosis exists and may be called "unicommissural dome-stenosis" (Figure VI-109d, e and f and VI-110b and c). In the latter, as the name implies, there is only 1 commissure in the aortic valve (Edwards, 1958).

Such a valve may be viewed as having but 1 cusp which is so constructed as to give the orifice the shape of an exclamation mark. The narrow part of the orifice is at the single commissure while the widest part lies opposite the commissure. The single cusp may be said to start at the aortic wall at the commissure and then extend across the orifice without making contact with the aortic wall; it then turns on itself to make a second connection with the aortic wall and so to create the single commissure (Figures VI-109d, e and f and VI-110b and c). In both the simple and the unicommissural varieties of dome-stenosis of the aortic valve, the raphe extend from the aortic wall onto the aortic base of the deformed

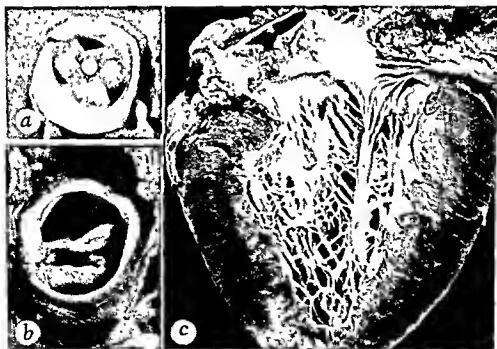


Figure VI-110. Congenital aortic stenosis. *a*. Simple dome-shaped aortic stenosis viewed from above. Probe lies in the narrow aortic orifice. From a boy 2½ years old. (From DuShane and Edwards, 1954. Reproduced with permission.) *b* and *c*. Unicommissural aortic stenosis from a boy 3 years old. *b*. The valve as viewed from above. The commissure is at the left. At the opposite wall, a valvulotomy has been done, producing two flaps which are not attached to the lateral wall of the aorta. *c*. The aortic valve has been opened through the single commissure. The site of the valvulotomy is in the center of the illustration of the aortic valve. Beneath the valve, the left ventricular endocardium shows conglomerate endocardial thickening. This may represent either primary thickening of the endocardium or regurgitant lesions from the coexisting aortic insufficiency.

leaflet. Although these raphe may be looked upon as representing abortive commissures, they do not usually extend far from the base toward the free edge of the valvular tissue. In this way the raphe constitute inadequate lateral supports for the valvular tissue to the aortic wall.

The left ventricle is considerably hypertrophied and may have endocardial thickening. In some instances the endocardial thickening as well as the aortic stenosis may represent *primary endocardial sclerosis*. At other times the endocardial thickening of the left ventricle may be the result of dilatation of the failing left ventricle, incident to the aortic stenosis, or it may represent a series of regurgitant (jet) lesions resulting from coexisting insufficiency of the stenotic aortic valve.

Incidence and Sex Distribution

The exact incidence of congenital aortic stenosis as a primary condition is difficult to judge. In the first place, some cases, especially those occurring in adolescents and adults, have been classified as representing acquired disease (Campbell and Kauntze, 1953). In the second place, in cases associated with endocardial sclerosis (Torp, 1951) it is often difficult to determine whether the aortic stenosis is simply an integral part of a primary endocardial sclerosis or the endocardial sclerosis is secondary to a primary aortic stenosis. In the pathologic collection of more than 550 specimens at the Mayo Clinic, 6 are thought to represent primary congenital aortic stenosis. In 3 of these the lesion is of the simple dome-shaped variety (2 of the cases were reported by DuShane and Edwards, 1954) and in the other 3 it is of the unicommissural dome-shaped type. The sex distribution slightly favors the male.

Functional and Clinical Features

(See reviews by Marquis and Logan, 1955, and by Downing, 1956). The primary disturbance in congenital aortic stenosis (as in the acquired type of stenosis) is obstruction to output of the left ventricle. Elevation of left ventricular pressure with a differential in pressure between the left ventricle and the systemic arterial circulation is the essential physiologic means of determining the diagnosis. Symptoms of coronary insufficiency may also be evident, especially in patients old enough to relate their symptoms.

Aortic insufficiency probably coexists with congenital stenosis, because the congenitally stenotic

aortic valve has essentially a fixed orifice throughout the cardiac cycle. During diastole, differential in pressure between the aorta and left ventricle is greater than between the pulmonary artery and the right ventricle. As a result, there is greater likelihood that patients with aortic stenosis of the dome-shaped variety will have significant aortic insufficiency than there is that patients with a similar deformity involving the pulmonary valve will have pulmonary insufficiency. The features of obstruction to left ventricular output may be duplicated by subaortic stenosis which is an important condition to be considered in the differential diagnosis. Also, the rare primary constriction of the ascending aorta, so-called *supravalvular aortic stenosis* (Chen *et al.*, 1957), may yield clinical features indistinguishable from those of obstruction at or below the aortic valve. In patients having severe aortic obstruction, the functional derangement may in part resemble that in aortic atresia in that a left-to-right shunt may occur through the foramen ovale (Brown, 1934).

Complications and Prognosis

The major complications of congenital aortic stenosis are those of left ventricular failure and sudden death, the latter presumably from coronary insufficiency. The age at death is difficult to determine because of the tendency to regard aortic stenosis of adolescents and adults as acquired. This explains the opinion that, in general, congenital aortic stenosis probably is responsible for death during infancy and childhood more often than at older ages. The oldest patient with congenital aortic stenosis, diagnosed by the author from the pathologic specimen of the Mayo Clinic was a girl, 16 years of age. Campbell and Kauntze (1953) reported the occurrence in a girl 15 years of age, and in a boy 11 years old, of a stenotic aortic valve that resembled the valve of congenital pulmonary stenosis. Kiloh's (1950) report, dealing with patients less than 50 years of age who had aortic stenosis, implied that in some the disease may have been congenital.

Surgical Correction

Aortic valvulotomy may relieve the aortic obstruction. Because of the nature of the valve, this procedure may accentuate the coexisting aortic insufficiency (Marquis and Logan, 1955; Edwards, 1958).

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Congenital Malformations

E. Malformations of Endocardium and Pericardium

JESSE E. EDWARDS

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ENDOCARDIAL SCLEROSIS

Endocardial sclerosis is the term applied to fibrous thickening of the mural endocardium. Two basic forms are recognized: primary and secondary. The secondary type is seen in chambers proximal to atretic or severely stenotic valves and in chambers that are dilated for any reason. Endocardial thickening is usually less severe in the secondary form than in the primary. Primary endocardial sclerosis may have no associated condition or may be associated with valvular stenosis which is thought to be part of the endocardial disease.

Pathologic Anatomy

Primary endocardial sclerosis has also been designated as "endomyocardial sclerosis" and "endocardial fibroelastosis." (For reviews, see Gross, 1941; Cosgrove and Kaump, 1946; Craig, 1949; Dennis *et al.*, 1953; Rosahn, 1955; Black-Schaffer, 1957). The left ventricle is primarily involved. The mural endocardium is thickened, gray and glassy, and the prominences of the papillary muscles are indistinct. In some cases the endocardial thickening is restricted to the mural endocardium, while others have associated thickening of one or more valves and stenosis of the orifices of these valves. When the valves are involved, it

may be difficult or impossible to be certain of the classification. It may also be impossible to decide whether all of the endocardial changes occurred simultaneously and so represent primary endocardial sclerosis or whether the valvular changes occurred first and the thickening of the mural endocardium secondarily.

In some cases, obviously thick endocardial tissue fuses with thickened and shortened chordae. Such changes are indicative of the primary type. The thickening of the endocardium is caused by heavy deposits of collagenous and elastic tissue fibers (Figure VI-111a, b and c). The histologic changes in the myocardium include dilatation of the myocardial sinusoids, focal calcification (Figure VI-111d and e), and extension of the endocardial fibrous tissue into the sub-endocardial layers of the myocardium. Other nonspecific changes, such as "cloudy swelling," vacuolization of the myocardial fibers and minor degrees of lymphocytic infiltration, have been described. Evidence of acute inflammation is not found. The left atrium usually shows changes similar to those in the left ventricle. Right ventricular involvement is usually not present without left-sided involvement. When present, left atrial or right ventricular endocardial sclerosis may be secondary to the effects of the primary changes in the left ventricle. In

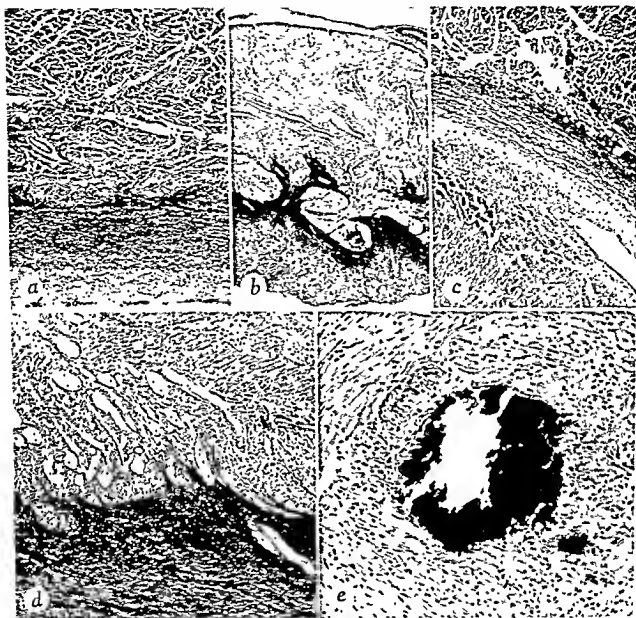


Figure VI-111. The left ventricle in primary endocardial sclerosis. (a-d, stained with Verhoeff's elastic tissue stain and counterstained with van Gieson's connective tissue stain, El-v.G.) a. Thickening of mural endocardium with elastic tissue and collagen. X 60. From a child 1½ years old with dilated primary endocardial sclerosis. The heart is illustrated in Figure VI-113. b. Marked thickening of endocardium by collagen and elastic tissue which extend into the underlying muscle. From a newborn infant with the contracted type of primary endocardial sclerosis. See d and e for other illustrations in the same case. X 11. c. Focal mural thrombus showing thickened endocardium. Other illustrations of this case in a and Figure VI-113. X 45. d. Beneath the thickened endocardium are prominent dilated myocardial sinusoids. See b and e for other illustrations of this case. e. Focal calcification in myocardium in a newborn infant with the contracted type of primary endocardial sclerosis. (Illustrations b, d and e are taken from a case of the contracted type of endocardial sclerosis observed in the newborn by Drs. Louise Wiegstein, S. W. Lippincott and H. D. Clippis of Seattle, Washington. The illustrations were prepared and reproduced with their permission.) Hematoxylin and eosin. X 145.

many but not in all cases, the foramen ovale is sealed.

In rare cases a peculiar localization of fibrous tissue in the left atrium just above the mitral valve may cause obstruction in the lowermost part of the atrium (supravalvular stenosis of left atrium)

(Rogers *et al.*, 1955). The lesion has been interpreted as secondary to concomitant mitral insufficiency. When the valves are thickened, they are composed of loose and dense collagenous and elastic tissue fibers (Figure VI-111a, b and c). The been compared to embryonic tissue. Vasculariza-

tion, fibrosis and cellular infiltration which might indicate an inflammatory basis are usually not encountered.

Depending on the appearance of the left ventricle, primary endocardial sclerosis may be subdivided into the dilated type and the contracted type.

Dilated Type of Endocardial Sclerosis. As the name implies, the left ventricular wall is dilated and usually is noticeably hypertrophied as well (Figure VI-113). The cardiac weight may be 3 to 4 times normal for the age of the patient, the increase in weight being mainly on the basis of the left ventricular hypertrophy. Focal thrombi in various stages of organization may be adherent to the dilated wall of the left ventricle (Figure VI-111c). Some of the cases reported as examples of *congenital idiopathic hypertrophy* show the characteristic features of the dilated type of primary endocardial sclerosis (Kugel and Stoloff, 1933, Levine, 1934; Kugel, 1939; Cosgrove and Kaump, 1946; Glynn and Reinhold, 1950) and should be so classified. The large dilated left ventricle with endocardial thickening, which is commonly seen when the left coronary artery arises from the pulmonary trunk (as in one of the cases of Craig, 1949), resembles the appearance of the left ventricle in the dilated type of primary endocardial sclerosis.

Contracted Type (Constrictive Endocardial Sclerosis). In the contracted type, the left ventricle is small, both in its absolute size and in relation to the size of the right ventricle. The right ventricle is dilated and greatly hypertrophied (Figure VI-114a and b). The disparity in size between the two ventricles makes the left appear as a mere appendage of the right. The left ventricular endocardium is diffusely thickened and may measure more than 1 mm. in thickness. It is pale gray and at times grossly resembles cartilage. The left atrium may be dilated and its endocardium may show a moderate degree of diffuse thickening. As in the dilated type, the valves may be normal or thickened.

Incidence and Sex Distribution

In recent years, it has been claimed that endo-

cardial sclerosis is commoner than was formerly thought. Rosahn (1955) found only 4 cases among 269 necropsies on children less than 2 years of age. Among 54 necropsies on infants and children who had congenital cardiac disease, Lambert and associates (1953) found that the most frequent anomaly was complete transposition of the great vessels (20 cases) and that endocardial sclerosis was the next most common condition (15 cases). Among somewhat more than 550 specimens in the pathologic collection of the Mayo Clinic there are 25 cases. In conditions like ventricular septal defect, patent ductus arteriosus and aortic coarctation, secondary endocardial sclerosis is common and should not be interpreted as representing primary endocardial sclerosis.

The sex distribution is about equal, as judged from the compilation of 149 cases from the literature by Dennis and associates (1953). Some of Dennis' cases, however, had associated valvular atresia and so are properly to be classified as secondary endocardial sclerosis.

Functional and Clinical Features

The basic functional disturbance in primary endocardial sclerosis is *restriction of left ventricular function*. By angiocardiographic studies, Linde and associates (1958) demonstrated that throughout the cardiac cycle the left ventricle does not change in size or contour. This phenomenon constitutes a barrier to left ventricular filling and so causes an elevation of left atrial pressure.

With respect to the contracted type, the sug-

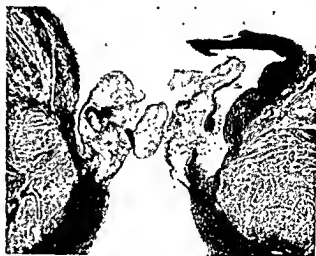


Figure VI-112. Photomicrograph of left ventricle and aortic valve in endocardial sclerosis of primary type with coexistent aortic stenosis. The left ventricular mural endocardium and aortic valvular tissue are thickened. (From a case submitted by Dr. Frank P. Falsetti.) Elastic tissue stain. X 10.

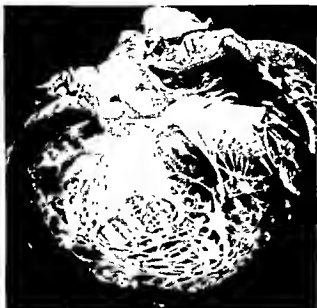


Figure VI-113. Left ventricle in the dilated type of primary endocardial sclerosis. From a female infant 1½ years old. Photomicrographs from this case appear in Figures VI-111a and c.

gestion was made, in 1946, to the author by Dr. H. B. Burchell that the thickened endocardium binds (constricts) the left ventricle in a relatively contracted state. In the dilated type of endocardial sclerosis, the angiocardigram (Prec and Cassels, 1952) reveals delayed emptying of the left ventricle. The basis for this may be the thickening of the endocardium which prevents complete emptying of the left ventricle during systole (Lunde *et al.*, 1958). The residual blood volume, therefore, acts as an obstructive factor to the flow of a normal amount of blood into the left ventricle.

In either type of primary endocardial sclerosis, there is strong evidence for elevation of left atrial pressure. Even when not associated with valvular disease, endocardial sclerosis causes functional changes in the pulmonary circulation similar to those seen in mitral stenosis.

When mitral stenosis or insufficiency is associated with endocardial sclerosis, the secondary changes of pressure in the pulmonary circulation are not basically altered from the situation in which valvular disease is absent. In *catheterization studies* in endocardial sclerosis and mitral valvular disease, Mannheim and associates (1952) and Maxwell and Young (1954) found elevation of pulmonary arterial wedge pressures. When aortic stenosis is associated with primary endocardial sclerosis, elevation of left atrial pres-

sure is dependent on a combination of the primary effects of the endocardial sclerosis and, in addition, on any left ventricular failure that might result from the aortic valvular stenosis. Coronary insufficiency may be an additional feature in patients having aortic stenosis. The elevation of pulmonary venous and capillary pressure in all cases of primary endocardial sclerosis makes pulmonary edema a constant possibility.

The clinical features in endocardial sclerosis have been reviewed (Adams and Katz, 1952; Blumberg and Lyon, 1952; Dennis *et al.*, 1953; Lambert *et al.*, 1953; Rosahn, 1955). The symptoms are nonspecific and are similar to those in other forms of acyanotic congenital heart disease causing primary pulmonary venous obstruction (cor triatriatum) and left ventricular failure, as for example, in ventricular septal defect, aortic coarctation, patent ductus arteriosus, anomalous origin of the left coronary artery from the pulmonary trunk, glycogen storage disease and interstitial myocarditis (Rosenbaum *et al.*, 1953). Symptoms are usually present in infants less than 1 year of age. The findings often include poor feeding, failure to gain properly, dyspnea without cyanosis, cardiac enlargement, absence of significant cardiac murmurs, and recurrent pulmonary edema and bronchopneumonia. If valvular disease is associated, the murmur of the particular valvular disease may be heard.

Electrocardiographically Vlad and associates (1955) frequently found either left ventricular strain or right ventricular hypertrophy, and sometimes both. Alterations of the P waves were common, indicating either right or left atrial dilatation or hypertrophy. Complete heart block occurs occasionally (Stadler *et al.*, 1950).

Complications and Prognosis

The major complications are concerned with the consequences to the lesser circulation: pulmonary edema with or without complicating bronchopneumonia, and right ventricular failure. In cases of the dilated type, left ventricular mural thrombi may occur. These may serve as foci from which systemic embolism occurs. Patients rarely survive to childhood.

In recent years the claim has been made that this condition is seen in adult life. Relatively mild left ventricular endocardial sclerosis in adult life is probably acquired and secondary to cardiac failure, at times from chronic myocarditis. The author doubts that a congenital form exists in adults; if it does exist, it is probably mild and not likely to be responsible for cardiac failure.

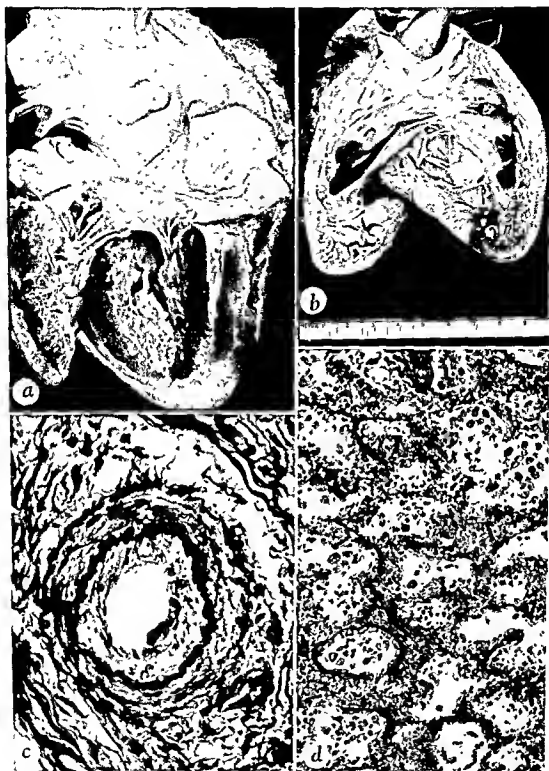


Figure VI-114. The contracted type of primary endocardial sclerosis (constrictive endocardial sclerosis) in a boy 5 years of age who died of congestive cardiac failure. *a.* The left side of the heart. The endocardium of the left ventricle is thickened and trabeculated. The left atrium is dilated. The mitral valve is normal. *b.* The right ventricle. Marked dilatation and hypertrophy. This illustration is reduced to a greater extent than *a.* *c.* Small intrapulmonary artery showing medial hypertrophy and intimal fibrosis. (El-vG; X 340.) *d.* Lung. The alveolar walls are thickened, mainly on the basis of capillary engorgement. Prominent fibers of elastic tissue are in the alveolar walls. Intra-alveolar hemosiderin-laden macrophages. (El-vG, X 140.)

Developmental Basis

Rosahn (1955) comprehensively reviewed the various theories for the developmental basis of endocardial sclerosis. Although fetal endocarditis was at one time the most widely held theory, he

agrees with Gross (1941) that supportive evidence for this belief is lacking. He rejected theories concerned with maternal infection, mechanical factors, collagen disease, anoxia and improper development of the bulbus cordis. He favored a genetic basis for endocardial sclerosis.

ABSENCE OR DEFECT OF PERICARDIUM

The subject of congenital pericardial defect was reviewed by Sunderland and Wright-Smith (1944). The pericardium may be entirely absent or only a portion of it may be involved in the defect. When a portion of the pericardium is defective, the defect usually lies on the left side. When the entire pericardium is absent, the heart and left lung lie in the same serous cavity.

Usually no symptoms result from this malformation but, in rare cases, strangulation of all or a portion of the heart may occur. In one instance (Sunderland and Wright-Smith) the left ventricle herniated through a defect, resulting in strangulation which was thought to be the cause of death. A similar condition was reported by Boxall (1886). In a specimen seen by the author (Edwards, 1954), the pericardium was defective on the right side and a portion of the right ven-

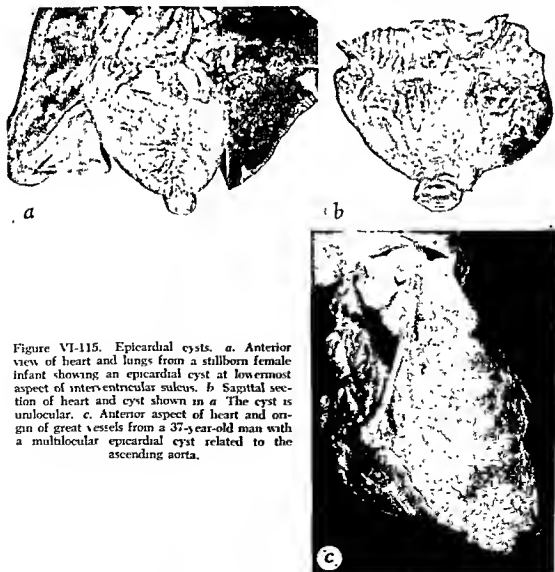


Figure VI-115. Epicardial cysts. *a*. Anterior view of heart and lungs from a stillborn female infant showing an epicardial cyst at lowermost aspect of interventricular sulcus. *b* Sagittal section of heart and cyst shown in *a*. The cyst is unilocular. *c*. Anterior aspect of heart and origin of great vessels from a 37-year-old man with a multilocular epicardial cyst related to the ascending aorta.

tricle had herniated through it. In a report of absence of the pericardium, Shafiroff (1951) re-

viewed the surgical anatomy of the phrenic nerve in this condition.

CYST AND DIVERTICULUM OF PERICARDIUM

The subject of cysts and diverticula of the parietal pericardium was extensively reviewed by Lillie and associates (1950). Presumably, congenital solitary lesions occur in relation to the pericardium. These usually are asymptomatic and are discovered accidentally on roentgenographic examination of the thorax. The lesions most commonly occur in the cardiophrenic angle, more commonly on the right than on the left side. Some are simply diverticula of the pericardium and, therefore, communicate with the pericardial cavity (Bishop *et al.*, 1950). In other instances, solitary multilocular cysts contain clear watery material. The cysts are lined by a single layer of flat cells. Lillie and associates thought

that such cysts and diverticula are developmentally related and represent persistence of the ventral parietal recess of the pericardium.

The lesions are benign and usually do not produce symptoms. When they are encountered surgically, removal is relatively simple.

Even more uncommon than cysts related to the parietal pericardium are cysts of the epicardium. The author has observed in a stillborn infant, a unilocular cyst that involved the lowermost portion of the epicardium in relation to the interventricular sulcus (Figure VI-115a). In another instance, a 37-year-old man had a multilocular cyst attached to the visceral pericardium overlying the ascending aorta (Figure VI-115b).

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Congenital Malformations

F. Malformations of the Coronary Vessels

JESSE E. EDWARDS

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ANOMALOUS ORIGIN OF CORONARY ARTERIES

ANOMALOUS ORIGIN of the coronary arteries may be divided into two categories. In the first, the coronary arterial supply is derived exclusively from the aorta but the origin deviates from the normal pattern. In the second group, one or both of the coronary arteries arise from the pulmonary trunk. The clinical features and functional characteristics of the two groups are profoundly different.

Anomalous Origin of Coronary Arteries from Aorta

SINGLE CORONARY ARTERY

According to Krumbhaar and Ehrlich (1938) and Roberts and Loube (1947), who reviewed the subject, Hyrtl set the criterion for a true single coronary artery by stipulating that the entire heart must be supplied by one coronary artery from which no conspicuous anomalous branches arise. Instances in which the usual 3 coronary arteries are present with only 1 coronary ostium in the aorta would then not be regarded as true examples of a single coronary artery. Krumbhaar and Ehrlich stated that the classification of single coronary artery should include vessels which have a single coronary ostium in

the aorta, as well as those which fulfill the postulate of Hyrtl. The report of Roberts and Loube covers an analysis of 31 cases of single coronary artery, including 9 cases of their own.

In addition to the type of single coronary artery which meets the stipulation of Hyrtl, there are 2 other patterns. In one, the single coronary artery gives rise to the right and left coronary arteries from which, in turn, the standard branches arise. The other pattern has a dimple at the expected location of the ostium of the absent coronary artery, and a small twig lies in the expected location of the absent artery. Collateral connections are present between the single artery and the branches of the hypoplastic twig. The branches of this small vessel are larger than the vessel itself. Such a case is probably one in which the 2 coronary arteries had formed normally but in which the ostium of one had become obliterated during fetal life. Collateral connections between ramifications of the 2 arteries are responsible for blood flow to the branches of the "absent" vessel. The latter type of pattern was observed 7 times among the 31 cases analyzed by Roberts and Loube. In 5 cases the left artery was the vessel without an aortic ostium. An essentially similar case, reported in 1948 by Reindell and Harnasch, had no left coronary ostium and no dimple at the ex-

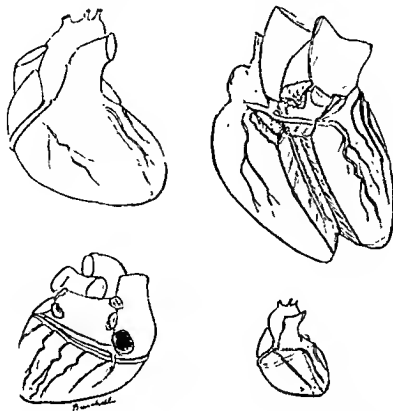


Figure VI-116. Burchell's case of single coronary artery in an adult. (Illustrations prepared by Dr. H. B. Burchell and reproduced with his permission.)

pected origin in the aorta. The right vessel was the single artery.

In an occasional case of anatomic tetralogy of Fallot, the author has observed a somewhat similar arrangement in which the ostium of 1 of the 2 coronary arteries, though present, was stenotic. Reference has been made (page 322, Figure VI-49) to the large collateral vessels that may cross the outflow tract of the right ventricle in such cases.

Knop and Bennett (1944) reported an instance of a single coronary artery arising from the right aortic sinus in a male infant aged 5 days. In Figure VI-116 is illustrated a case of single coronary artery which was observed by Dr. H. B. Burchell in the Department of Pathology of the University of Toronto in 1934. This was an incidental finding in a male adult. The single coronary artery arose from the right aortic sinus, and shortly after its origin gave rise to a branch which entered the ventricular septum. Seven of the 31 cases of Roberts and Loube also had other anomalies of the heart.

A single coronary artery without other cardiac malformations is a pathologic entity. Its functional significance is usually negligible unless it

is associated with serious acquired occlusive disease. In these circumstances, occlusion of the single artery would obviously be hazardous to the patient. With the report of a case of a single coronary artery by White and Edwards (1948), the number of reported instances of adults with this entity was brought up to 28. In 4 of these, myocardial infarction had developed. Under rare circumstances part or all of the coronary arterial system arises from the innominate artery (Bland *et al.*, 1933). In cases reported by Trevor (1912) and Cree (1956), the coronary arterial supply arose as a single branch from the innominate artery, mitral atresia, a single ventricle, and persistent truncus arteriosus were also present.

ORIGIN OF LEFT CIRCUMFLEX ARTERY FROM RIGHT CORONARY ARTERY

More common than single coronary artery, and perhaps the most common malformation of the coronary arteries, is origin of the left circumflex coronary artery from the right coronary artery. The anomalous artery arises from the proximal part of the right artery and passes behind the aorta to reach the left atrioventricular sulcus. It then follows the

usual course of this vessel. The artery arising from the left aortic sinus is the anterior descending coronary artery (Antopol and Kugel, 1933). In a study of 600 hearts from men, White and Edwards (1948) found this pattern in 2 cases. At times the right and left coronary arteries may arise from the same sinus of the aorta. The left circumflex and the anterior descending coronary artery may arise independently from the left aortic sinus, no common trunk of the left coronary artery being present.

Anomalous Origin of One or Both Coronary Arteries from Pulmonary Trunk

Origin of Both Coronary Arteries from Pulmonary Trunk is rare.

Tedeschi and Helpern (1954) and Alexander and Griffith (1956) each reported an instance in which both coronary arteries arose from the pulmonary trunk, unassociated with any other malformation. Tedeschi and Helpem quoted 4 other cases from the literature, 1 of which resembled their case, in the other 3, the hearts had additional serious malformations. Cases with origin of both coronary arteries from the pulmonary trunk have also been reported in association with the anatomic tetralogy of Fallot (Williams *et al.*, 1951).

Usually, only one coronary artery takes anomalous origin from the pulmonary trunk, and

the heart is otherwise normally developed. The left arises anomalously more commonly than does the right in a ratio of about 10 to 1 (Soloff, 1942, Kaumtz, 1947).

PATHOLOGIC ANATOMY

The anomalous artery arises from either the right or left pulmonary sinus, and then follows a normal course. The vessel has the histologic appearance of an artery although its media is relatively thin. Its lumen is either of normal caliber or dilated. The artery which arises from the aorta and its epicardial and myocardial branches may be wide and tortuous. Connections between the arteries may be demonstrated.

Dutra (1950) reported the rare occurrence of origin of a left coronary artery from the right pulmonary artery. The patient died at the age of 5 months, with evidence of myocardial ischemia in the region of the heart supplied by the anomalous vessel.

When the right coronary artery arises from the pulmonary trunk, the myocardium is usually normal. In anomalous origin of the left coronary artery, the myocardium may be normal, or may show acute or healed infarction comparable to infarction resulting from atherosclerotic coronary disease. Rupture of the left ventricle was observed by McKinley and associates (1951) in a 6-week-old child in whom the left coronary artery arose from the pulmonary trunk.



Figure VI-117. Anomalous origin of the anterior descending coronary artery from the pulmonary trunk. From a 37-year-old man who died of acute coronary insufficiency. *a*, Right ventricle (R.V.) and pulmonary trunk. The anterior descending coronary artery (A.D.) arises from the pulmonary trunk. *b*, Left ventricle (L.V.) and aorta. The right coronary (R.C.) artery and the left circumflex coronary artery (L.C.) arise from the aorta above the right aortic sinus. Except for the anomalous origin of the anterior descending coronary artery, the patient showed no other coronary arterial disease to explain the acute coronary insufficiency.

INCIDENCE AND SEX DISTRIBUTION

Denko and Hagerty (1953) indicated that only 52 cases of this condition had previously been reported. The pathologic collection of more than 550 specimens with congenital cardiac malformations in the Mayo Clinic contains 3 hearts with anomalous origin of a coronary artery from the pulmonary trunk (Figure VI-117).

FUNCTIONAL AND CLINICAL FEATURES AND PROGNOSIS

The explanation of myocardial ischemia, in anomalous origin of a coronary artery from the pulmonary trunk, has been disputed. Many have taught that it resulted from perfusion under low pressure of the myocardium by venous blood from the pulmonary trunk. The author (Edwards, 1958) has reviewed the basis for a contrary view, first suggested by Brooks in 1885 and supported by Abbott in 1927, which holds that the blood in the anomalous artery flows not from the pulmonary trunk but to the pulmonary trunk. The blood is derived from that coronary artery which arises from the aorta. The ischemia, therefore, results from an arteriovenous type of communication in the myocardium (Figure VI-118). The major support for this view comes from perfusion observations in postmortem specimens (Kittle

et al., 1955; Case *et al.*, 1958) and from the observation that, in the living anomalous artery, arterial-type blood flows toward the pulmonary trunk (Apley *et al.*, 1957).

The clinical picture has been reviewed (Bland *et al.*, 1933; Soloff, 1942; Eidlow and Mackenzie, 1946; Lyon *et al.*, 1946; Kammitz, 1947; Gasul and Loeffler, 1949). About two-thirds of patients whose left coronary artery arises from the pulmonary trunk die of the malformation during the first year of life. Usually symptoms do not appear before 3 months of age. Sometimes the patient has apparent discomfort (thought to be angina pectoris) during exertion, as while feeding.

The electrocardiogram may show changes typical of myocardial ischemia, or may have changes that are difficult or impossible to distinguish from those of endocardial sclerosis or other causes of left ventricular hypertrophy with heart failure. Patients with anomalous origin of the left coronary artery from the pulmonary trunk, who survive to adult life, may be unaffected by the malformation, or die from coronary insufficiency during relatively early adult life (Gouley, 1950; Figure VI-117).

Anomalous origin of the right coronary artery from the pulmonary trunk seems to be a benign condition (Jordan *et al.*, 1950).

ANOMALOUS COMMUNICATION OF CORONARY ARTERIES WITH A CARDIAC CHAMBER, PULMONARY TRUNK OR CARDIAC VEIN; "CONGENITAL ANEURYSM"

Valves Normal

Rarely, when both coronary arteries arise from the aorta and the cardiac valves are normal, a main coronary artery or a branch may communicate with a cardiac chamber, the pulmonary trunk or a cardiac vein.

The vessel may communicate either by a single or by multiple openings with a cardiac vein (Emminger, 1947), the coronary sinus (Halpert, 1930; Nagayo and Takahashi, 1932; Paul *et al.*, 1949; Davison *et al.*, 1955), the right atrium (Figure VI-119; Harris, 1937; Colbeck and Shaw, 1954; Valdivia *et al.*, 1957; Edwards *et al.*, 1958), the right ventricle (Trevor, 1912; Brown and Burnett, 1949; Espino Vela *et al.*, 1951; Davis *et al.*, 1956), left ventricle (Reid, 1922; Lovitt and Lutz, 1954), the left atrium (Mozen, 1956), or the pulmonary trunk (Figure VI-120;

Krause, 1865; Brooks, Case 2, 1885; Biorck and Crafoord, 1947; Scott, 1948; Baylis and Campbell, 1952). Such a communication simulates or functions as an arteriovenous fistula (Edwards, 1958). As in other arteriovenous fistulas, the artery leading to the abnormal communication is enlarged. It may be tortuous and show one or more saccular aneurysms. Branches of vessels not directly involved in the anomalous communication may be enlarged since they carry blood to the low pressure area.

In several cases in which one or both coronary arteries communicated with the pulmonary trunk, enlarged mediastinal arteries connected with those coronary vessels taking part in the anomalous pathway (Brooks, 1885; Biorck and Crafoord, 1947). When both coronary arteries arise from the aorta, and branches of one or both connect with the pulmonary trunk, the abnormal opening in the pulmonary trunk is usually single, and the

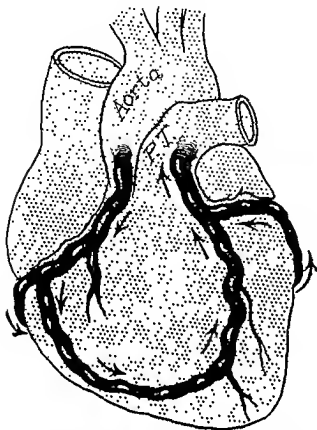


Figure VI-118. Diagrammatic representation of circulation in anomalous origin of the left coronary artery from the pulmonary trunk. Blood in the right coronary artery which is derived from the aorta is shunted to the anomalously arising left coronary artery by way of anastomoses between the two coronary arteries. From the left coronary artery blood is delivered to the pulmonary trunk (P.T.). The arteriovenouslike communication is thought to be responsible for the coronary insufficiency evident in cases of anomalous origin of a coronary artery from the pulmonary trunk.

vessel making the communication has at times been called an "accessory coronary artery."

The aneurysms which form in coronary arteries taking part in abnormal communications of the types under discussion have been called "congenital aneurysms." These are probably not primary aneurysms but rather are secondary to the effects of generalized dilatation of the involved artery. In spite of their secondary nature, sometimes these aneurysms are reported as representing a primary condition while the underlying arteriovenous-like communication receives only passing attention. The aneurysms may attain large proportions and may show secondary calcification in their walls and mural thrombi in their lumen. The calcification may be evident in the clinical roentgenogram (Colbeck and Shaw, 1954).

FUNCTIONAL AND CLINICAL FEATURES

The primary functional disturbance of the communication under discussion is the result of runoff of blood from the coronary arterial system. As in arteriovenous fistulas elsewhere in the body, the portion of the heart supplied by the vessel beyond the communication are

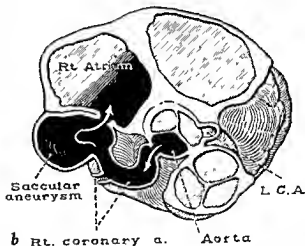
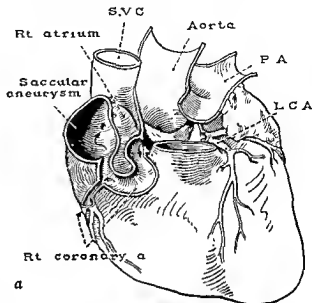


Figure VI-119. Anomalous communication of the right coronary artery with the right atrium in a woman 48 years old. (Edwards and associates, 1958. Reproduced with permission.) *a* Schematic portrayal of the anterior aspect of the heart and the proximal portion of the right coronary artery. Originating from the wide right coronary artery is a branch which becomes aneurysmal and communicates with the right atrium. Beyond the origin of the latter branch, the right coronary artery has a normal course and normal caliber. S.V.C. indicates superior vena cava; P.A., pulmonary artery; L.C.A., left coronary artery. *b* Schematic portrayal of base of heart showing the communication of an aneurysmal branch of the right coronary artery with right atrial chamber.

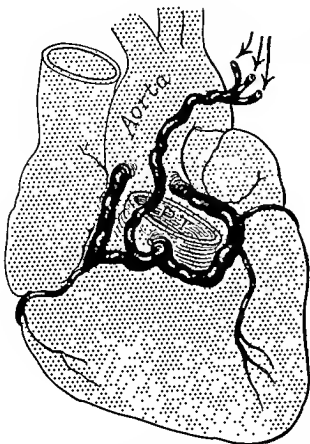


Figure VI-120 Anomalous communication of the two coronary arteries with pulmonary trunk. In this condition both coronary arteries arise from the aorta, but one or both connect with the pulmonary trunk. The opening of the pulmonary trunk may be regarded as an accessory coronary artery. By virtue of the low resistance of the pulmonary system, flow of coronary blood is directed toward this anomalous communication. Joining the coronary arterial system may be vessels derived from the mediastinum which in effect are collaterals to the coronary system.

ischemic, and the patient may suffer from coronary insufficiency.

If the vessel communicates with a cardiac chamber on the right side, a cardiac vein or the pulmonary trunk, cardiac catheterization may detect abnormally high oxygen concentration of the blood in the structure receiving the coronary artery (Davison *et al.*, 1955). When the vessel communicates with a left-sided cardiac chamber, there is runoff of coronary arterial blood, but no abnormality in oxygen saturation is detectable when the right side of the heart and the pulmonary arteries are catheterized. Retrograde aortography may demonstrate the communication (Gasul *et al.*, 1957; Morrow, 1957).

When the abnormal communication is into any

of the structures named except the left ventricle, a continuous murmur is often heard. Because of this feature, many of the reported cases had been clinically diagnosed as patent ductus arteriosus. Other conditions that must be considered in the differential diagnosis are rupture of an aneurysm of the aortic sinus into the right atrium or ventricle, ventricular septal defect with aortic insufficiency, and arteriovenous communication involving vessels of the thoracic cage, the subclavian or internal mammary vessels (Edwards *et al.*, 1958).

COMPLICATIONS AND PROGNOSIS

Some patients seem to suffer little from the effects of the abnormal communication, probably because they have only a small opening. The symptoms arise from 1 of 3 main complications (Edwards *et al.*, 1958): (1) congestive cardiac failure, (2) coronary insufficiency, and (3) intravascular bacterial infection developing in relation to the abnormal communication. In most reported cases, the patients lived to adult life; occasionally death may occur in infancy or childhood.

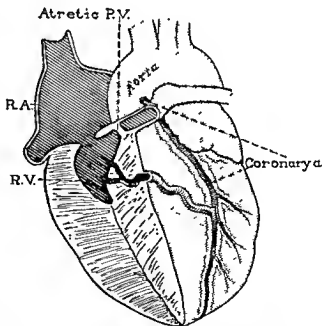


Figure VI-121. Origin of a vessel from right ventricle in a case of pulmonary atresia with intact ventricular septum and functioning tricuspid valve. The vessel arising from the right ventricle represents coalescence of right ventricular sinusoids. After emerging into the epicardium, this vessel makes communication with the normal coronary arteries. A similar situation may occur on the left side when the aortic valve is atretic, the ventricular septum is intact and the mitral valve functions as a competent valve.

SURGICAL THERAPY

Surgical treatment consists of obliterating the abnormal communication (Biorek and Crafoord, 1947; Davis *et al.*, 1956; Mozen, 1956).

DEVELOPMENTAL BASIS

From the developmental analysis of the coronary vascular system made by Grant (1926a), it is apparent that in the early stages of cardiac development the myocardium is nourished by blood which is brought to it through wide intertrabecular spaces. These exist in the myocardium and are continuous with the cardiac chambers. Later, the coronary veins and the coronary arteries develop and connect with the epicardial aspects of the intertrabecular spaces. Following this phase, the growth of the myocardium causes reduction of the size of the intertrabecular spaces to that of the caliber of capillaries. The intertrabecular spaces, however, maintain communication with the cardiac chambers and, therefore, represent in the adult the normal small communications that exist between the coronary arteries and the cardiac chambers.

In a case reported by the author and his associates (1958), the communication between the right coronary artery and the right atrium was regarded as a normal connection. The abnormality resides not in a connection between the coronary artery and the atrial cavity, but rather in the large size of the connection. Normally the communications should have been reduced to microscopic size. A similar view was expressed by Grant (1926b) concerning the abnormal communication between a coronary artery and a cardiac ventricle in a case previously reported by Wilson and Grant (1923-26).

Atresia of a Semilunar Valve

In the presence of an intact ventricular septum, atresia of a semilunar valve and a competent corresponding atrioventricular valve, myocardial sinusoids leading from the ventricle behind the atretic valve converge to form a single vessel which emerges into the epicardium. There the anomalous vessel joins branches of one or both coronary arteries (Williams *et al.*, 1951; Alexander and Green, 1952, Figure VI-121). The effects of the valvular atresia dominate the functional derangement.

ANOMALIES OF THE CORONARY SINUS

Dilatation of Coronary Sinus

This is usually associated with a persistent left superior vena cava. The condition is of no functional consequence, since blood from the left innominate vein is carried to the right atrium by way of the connection of the persistent left superior vena cava with the coronary sinus.

Atresia of Right Atrial Ostium of Coronary Sinus

Atresia of the right atrial ostium of the coronary sinus is to be distinguished from absence of the coronary sinus which occurs when a persistent left superior vena cava connects either with the left atrium or, more commonly, with the left aspect of a common atrium as in cor biloculare. The term *atresia of the right atrial ostium of the coronary sinus* is reserved for cases in which the coronary

sinus exists but its opening into the right atrium is sealed. The coronary sinus may then connect with a persistent left superior vena cava which, in the lower cervical region, makes a cross-connection with the right innominate vein, thus allowing cardiac venous blood to ascend along the left superior vena cava and then to be carried into the right atrium through the right superior vena cava (Grant, 1917; Harris *et al.*, 1927).

Even when a left superior vena cava is persistent, the size of this vein may be so narrow that it constitutes an ineffective channel. Under these circumstances, and in the absence of a left superior vena cava, blood from the coronary sinus is carried into the atria by means of enlarged thebesian veins. Fieldstein and Pick (1942) reported a case of the latter type and reviewed 5 other cases in the literature. Atresia of the right atrial ostium of the coronary sinus may occur as an isolated lesion, although more

TABLE VI-3

Cardiac Malformation or Persistent Left Superior Vena Cava in 9 Cases of Atresia of Right Atrial Ostium of Coronary Sinus

Case No	Associated Malformation	Persistent Left Superior Vena Cava
1	Atrial septal defect	0
2	None	0
3	Cor trilobular biatrium	+
4	Persistent common atrioventricular canal	0
5	Persistent common atrioventricular canal	0
6	Persistent common atrioventricular canal	+
7	Ebstein's malformation	+
8	Tricuspid atresia	0
9	Ventricular septal defect and pulmonary stenosis	0

commonly, in the author's experience, other cardiac malformations are associated with it. In only 1 of the 9 cases of atresia of the right atrial ostium of the coronary sinus which the author observed in the pathologic collection of the Mayo Clinic was there no associated malformation. Data on this case and the remaining eight are tabulated in Table VI-3, with the associated malformations and whether a left superior vena cava existed.

The basis for atresia of the right atrial ostium of the coronary sinus is not explained, though the usual association of a venous malformation is

an indication that the condition is established during intra-uterine life. Grant (1917) stated that the right atrial ostium of the coronary sinus probably closes at a time after the transverse branch between the superior venae cavae has been established. According to Grant, Hinton suggested that the basic cause for the atresia might be a large thebesian valve. In the presence of elevated right atrial pressure, the valve might be pressed into a closed position. With the connection between the superior venae cavae established, this closure causes no functional disturbance since the coronary blood would have an avenue of exit through the superior caval system. Secondary fusion of the enlarged thebesian valve with the wall of the right atrium might then follow.

Anomalous Communication between Coronary Sinus and Left Atrium

The subject of unusually large communication of the coronary sinus with the left atrium has been discussed under Interatrial Communications (page 275), since the functional derangements resemble those in atrial septal defect.

The developmental basis may depend on anomalous pulmonary venous connection to the primordia of the left superior vena cava from which the coronary sinus is derived. This condition may result from communication with the left superior vena cava of that part of the pulmonary venous system that becomes incorporated with the left atrium. Some support of this concept comes from clinical cases, like that of Mankin and Burchell (1933), in which catheterization studies show evidence both of anomalous pulmonary venous connection with the left superior vena cava and of communication of the left atrium with the coronary sinus.

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Anomalies of Coronary Sinus

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Congenital Malformations

G. Aneurysms of the Aortic Sinuses (Valsalva)

JESSE E. EDWARDS

ANEURYSMS OF THE aortic sinuses may be congenital or acquired. Those that are acquired result principally from bacterial endocarditis, and congenital aneurysms may become complicated by bacterial endocarditis (Jones and Langley, 1949). Thus, it is sometimes difficult to classify the underlying nature of the condition.

Pathologic Anatomy

Congenital aneurysms of the aortic sinuses usually are single. Micks (1940) reported on aneurysmal dilatation of the aortic sinuses. They represent a deficiency between the aortic media and the annulus fibrosus of the aortic valve (Edwards *et al.*, 1956). The two sinuses that most commonly are involved are the right and the posterior (noncoronary), but predominantly the right. The chamber in which an aneurysm of the aortic sinus will present depends on the relationship of the involved part of the sinus to other cardiac structures. Details of these were given by Edwards and Burchell (1957). Aneurysms of the right aortic sinus most commonly present in the outflow tract of the right ventricle, rarely in the right atrium (Oram and East, 1955, Figure VI-122). Aneurysms of the posterior aortic sinus present in the septal wall of the right atrium above the tricuspid valve.

Aneurysms classified as congenital probably are not present at birth but seem to develop at a congenitally weak portion at the junction of the heart and the aorta (Venning, 1951). When an aneurysm occurs in the right aortic sinus, a ventricular septal defect is commonly present immediately subjacent to the aneurysm.

Aneurysms restricted to the left aortic sinus

are rare. Oram and East (1955) have credited Higgins (1934) with reporting an aneurysm of the left aortic sinus which ruptured into the right atrium. Herson and Symons (1946) interpreted Macleod's (1944) case similarly. Review of these 2 reports makes it doubtful that they were correctly interpreted. The use of different terminology for the aortic sinus from that employed at present makes an exact interpretation impossible. Nevertheless, it is probable that both in Higgins' and Macleod's cases the aneurysms originated in the posterior (noncoronary) aortic sinus. In the case reported by Raman and Menon (1949), a 29-year-old man had aneurysms of the right and left aortic sinuses. Neither aneurysm had ruptured. The aneurysm of the left sinus presented in the epicardium medial to the left auricular appendage.

In arachnoidectasy (Marfan's syndrome), dilatation of the 3 aortic sinuses may be demonstrated by aortography (Steinberg and Geller, 1955).

Incidence

The lesion is uncommon. In 1949 Jones and Langley, reviewing literature and their own material, found only 25 cases.

Functional and Clinical Features and Prognosis

Rupture of the aneurysm usually causes a fistula with a left-to-right shunt between the aorta and the right ventricle or right atrium. Rupture usually occurs in adult life, commonly in the third and fourth decades.

In the clinical case of Fowler and Bevil (1951), a 4-year-old girl was alive 10 months after evidence of rupture of an aortic sinus aneurysm. Warthen's (1949) case of ruptured aneurysm of the right aortic sinus was unusual in that the aneurysm burrowed downward in the ventricular septum and then communicated with the left ventricle. The resulting clinical picture resembled aortic valvular insufficiency. In the case

Congenital Malformations

H. Malformations of Aortic Arch System

JESSE E. EDWARDS

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DUCTUS ARTERIOSUS

THE DUCTUS ARTERIOSUS* is of clinical significance under one of three conditions: (1) if it is associated with other cardiovascular malformations; (2) if it takes part in the formation of a vascular ring that interferes with the function of either the trachea or the esophagus; or (3) if, in the absence of other cardiovascular malformations, it remains patent. Patency of the ductus arteriosus, in the absence of other malformations, is variously called patent ductus arteriosus, persistent patent ductus arteriosus, or uncomplicated patent ductus arteriosus.

Patent Ductus Arteriosus

POSTNATAL CLOSURE

During the last trimester of pregnancy, the

*The term "ductus Botalli" is frequently applied to the ductus arteriosus but, according to Franklin, the ductus arteriosus was first described by Galen and not by Botallo (see Gilchrist, 1945).

ductus of the fetus shows intimal ridges which normally set the stage for eventual anatomic closure (Swensson, 1939, Jager and Wollenman, 1942). At the time of birth and shortly thereafter, the normal closing ductus has a cordlike structure. Its media contains microcysts of mucoid material and eccentric proliferation of muscle, while the intima is thick and is composed of laminated collagen and elastic tissue. The internal elastic lamina may be interrupted. The ductus that remains abnormally patent has a thin wall. In adults, the media of the patent ductus contains much collagen intermingled with the muscular tissue, and the intima is thin (Figure VI-123a).

Time of Normal Anatomic Closure. Gibson (1900) stated that the ductal lumen usually is entirely obliterated within 8 days from the time of birth. In contrast, Gilchrist (1945) stated that Alvarenga did not find a single example of perfect closure of the ductus ar-

teriosus in 54 infants whose ages ranged up to 1 month, and that Christie found the ductus still patent in 65 per cent of infants 2 weeks old. Wells (1908) stated that in many normal infants the ductus arteriosus may remain patent up to 3 to 6 weeks after birth, although it usually closes earlier. My own experience indicates that the ductus arteriosus as an effective channel is usually closed by the end of the second week after birth. At that time, the ductal wall is thick and cordlike and, although it may be possible to pass a narrow probe through the lumen, the channel is usually so narrow that it has no functional significance.

Persistent patency of the ductus arteriosus, according to Dr. Bradley M. Patten, may be regarded as an arrest in a fundamental process of growth. The cause for this failure is not known, although there is an interesting and probably significant relationship between it and the occurrence of maternal rubella during the first trimester of pregnancy (Swan, 1944, Swan *et al.*, 1946, Wesselhoeft, 1949). It is probable that a variety of factors are concerned in the appearance of patent ductus arteriosus as well as other congenital cardiac malformations (Campbell, 1949). If the ductus is not closed within 2 months after birth, it probably will remain patent in most cases. Delayed closure during childhood seems

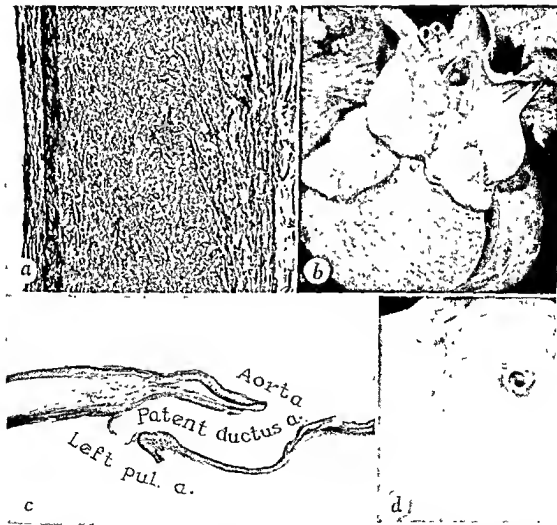


Figure VI-123. *a*. Aortic end of funnel type of patent ductus arteriosus, from a woman aged 73 years. The intima, which lies to the left, is very thin and is separated from the media by a layer of elastic tissue. Other illustrations from this case appear in *c* and *d*. (E1-vC. X 100.) *b*. Cylindrical type of patent ductus arteriosus, from a female infant who died at 9 months of age from cardiac failure. Another illustration from this case appears in Figure VI-121*c*. *c*. Funnel type of patent ductus arteriosus, from a woman aged 73 years. (E1-vC. X 24.) *d*. The pulmonary end of a patent ductus arteriosus. The ductus protrudes into the lumen of the left pulmonary artery. Other illustrations of this case appear in *a* and *c*.

possible, but would be unusual (Gilechrist, 1945; Burchell, 1948).

PATHOLOGIC ANATOMY

In rare instances the ductus arteriosus is a *right-sided* structure, running between the right pulmonary artery and the aorta. Usually it arises in the left pulmonary artery and inserts into the aorta just beyond the origin of the left subclavian artery (Figure VI-123b). Often it appears to arise from the bifurcation of the pulmonary trunk, but the statement that it originates from the bifurcation of this vessel may be shown to be incorrect from a developmental point of view, and by careful anatomic study.

Anatomic Types. Patent ductus arteriosus may be classified into (1) cylindrical, (2) funnel, and (3) window types. The cylindrical type, which is the most common (Gilechrist, 1945), possesses a relatively uniform caliber throughout its length, though the pulmonary end may be somewhat narrower than the aortic end. The funnel type is characterized by a wide aortic ostium and a lumen that tapers toward the pulmonary end. In some cases of the funnel type, the lumen is sufficiently wide to allow a shunt of significant magnitude; in other cases, the width of the pulmonary ostium is only 1 to 3 mm. and the patency of the ductus is of no functional importance (Figure VI-123c). In some of the latter cases, the pulmonary end of the ductus may be the seat of a bland thrombus which may protrude into the lumen of the left pulmonary artery. The window type of patent ductus arteriosus is of surgical importance. It is the least common and is usually found in relatively older patients. In this type the lumina of the aorta and the left pulmonary communicate directly, and the ductus arteriosus has no recognizable length. The surgical problems in ligating such an opening are obvious.

This type was found in 17 per cent of 60 persons 17 years of age or older (Keys and Shapiro, 1943). The author believes that the window type develops gradually. Evidently, as the pulmonary arterial system dilates because of the shunt, the pulmonary side of the ductus arteriosus is grad-

ually effaced, being incorporated into the gross structure of the left pulmonary artery.

While the window type of ductus arteriosus cannot be said to have length, the cylindrical and funnel types have a length usually of less than 10 mm. but sometimes up to 20 mm. (Wells, 1908). The diameter of the ductus after death is frequently from 3 to 6 mm. Gilechrist stated that, during life, the patent ductus may be observed to be as wide as the aortic arch.

Potts and associates (1949) noted at operation a patent ductus that had an outside diameter of 18 mm. Taylor and associates (1950) found that the patent ductus arteriosus at operation had an outside diameter ranging from 7.5 to 13 mm. (average, 10 mm.) and an approximate length ranging from 6 to 10 mm. (average, 8 mm.). In all but one case, the outside diameter of the ductus arteriosus exceeded the length. In the classic variety of patent ductus arteriosus, the pulmonary end of the patent ductus arteriosus may protrude as a nipple (Figure VI-123d) into the lumen of the left pulmonary artery.

Functional Effects on Pathologic Anatomy. Especially in classic ductus arteriosus, the stream (representing a left-to-right shunt) has a traumatizing effect on the wall of the left pulmonary artery opposite the pulmonary ostium of the ductus, and produces a localized patch in which the intima is thickened by collagenous and elastic tissue (Figure VI-124a). This lesion has long been recognized. On the basis of the suggestion made by Dr. Howard B. Burchell, my associates and I call this patch a *jet lesion*. Such lesions are also seen in experimental animals in which an artificial ductus arteriosus has been established (Leeds, 1918; Ross and Murphy, 1949). The lesions are not atheromatous and should not be confused with foci of true atheroma in the greater pulmonary arteries.

The chambers of the heart may exhibit changes, depending on the functional type of patent ductus arteriosus. In the classic type, in which the pulmonary pressure is not elevated and only a left-to-right shunt exists, the left ventricular chamber is dilated and the wall shows some hypertrophy (Figure VI-124b). The left atrium also may be dilated. The endocardium of both chambers may be thickened.

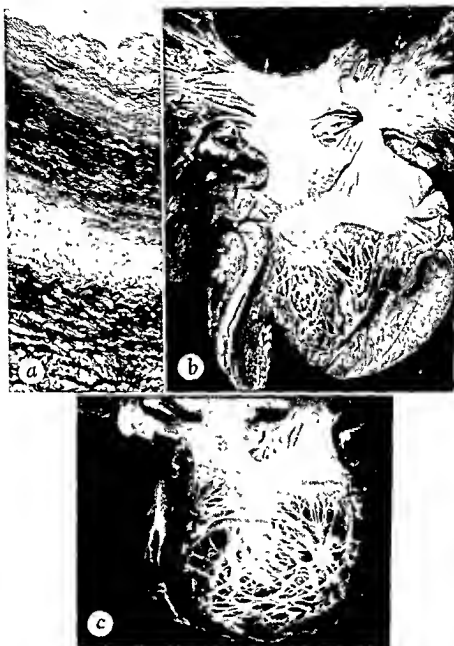


Figure VI-124. *a.* Left pulmonary artery in a case of classic patent ductus arteriosus in which ligation of the ductus had been performed $4\frac{1}{2}$ years before death. The intima is greatly thickened, in part by elastic tissue. The concentration of elastic tissue appearing in the upper part of the figure is separated from the media by a layer of collagen. (EI-VG, X 125.) (From Dry, Harrington and Edwards, 1948.) *b.* The pulmonary veins and the left side of the heart, in a man aged 24 years with classic patent ductus arteriosus. The pulmonary veins are dilated. Endocardium is thickened in the dilated left atrium and the left ventricle is dilated and hypertrophied. *c.* The left atrium and left ventricle in widely patent ductus arteriosus, from an infant who died at 9 months of age from cardiac failure. Dilatation of the left ventricle and left atrium. Note prominent endocardial thickening of the left atrium and left ventricle. Another illustration from this case appears in Figure VI-123*b*.



Figure VI-125. Pulmonary arterial vessels in patent ductus arteriosus with pulmonary hypertension. *a* Cross section of a muscular pulmonary artery and longitudinal section of an arteriolar branch. From a male infant 1 year, 10 months of age. Medial hypertrophy, no intimal lesions (Elastic tissue stain, X450.) *b*, Large muscular artery from a 6½-year-old girl who also had a large ventricular septal defect. Nonspecific intimal fibrous thickening has caused obliteration of the lumen. The medial layer is hypertrophied. (Elastic tissue stain, X140.) *c* Cross section of a large muscular artery and longitudinal section of its small arterial branch. At the origin of the small artery the lumen is occluded by a "plexiform lesion." The medial layer of the parent vessel is hypertrophied. From a 23-year-old woman (Hematoxylin and eosin, X90.) (From Edwards, 1955. Reproduced with permission.)

Patients with a wide patent ductus arteriosus and pulmonary hypertension have a bi-ventricular hypertrophy, the thickness of the right ventricle approximating that of the left ventricle. During the stages when a left-to-right shunt is dominant, the left ventricular and left atrial chambers may be dilated. The

endocardium of these chambers become thickened (Figure VI-124c). Later, when the volume of the left-to-right shunt falls off, the left-sided chambers may become reduced in size, but the endocardial thickening and the right ventricular hypertrophy remain.

Pulmonary Vascular Bed. Structural

changes may be present in the pulmonary vascular bed in patients with patent ductus arteriosus. In patients with normal pulmonary arterial pressures, the pulmonary vascular structure is normal (Heath and Whitaker, 1955). This is comparable to the situation in small ventricular septal defect.

Patients with pulmonary hypertension early have medial hypertrophy of the arteries and arterioles. Later, occlusive intimal lesions, exactly like those in large ventricular septal defect, make their appearance (Edwards, 1955; Whitaker *et al.*, 1955; Heath and Edwards, 1958, Figure VI-125). The complicating intimal lesions are associated with rising and, ultimately, relatively fixed pulmonary vascular resistance (Heath *et al.*, 1958a).

INCIDENCE AND SEX DISTRIBUTION

It is difficult to determine the exact incidence of patent ductus arteriosus relative to other malformations from necropsy findings because of the many successfully treated patients. Abbott (1925) noted 67 examples of patent ductus arteriosus among 555 cases of clinically significant malformations. The condition is fully as common as ventricular septal defect. It has a distinct preference for female patients, the ratio of females to males being about 3 to 1 (Gross, 1952; Cosh, 1957).

FUNCTIONAL AND CLINICAL FEATURES

The basic disturbances in function among patients with patent ductus arteriosus are similar to those among patients with ventricular septal defect (Edwards, 1957).

During fetal life the flow is from the pulmonary arterial bed to the aorta. In normal mammals, immediately after birth, the fall in pulmonary vascular resistance produces a left-to-right shunt (Ardran *et al.*, 1952). This may persist until the ductus closes anatomically.

As in ventricular septal defect, the effects of patency of the ductus arteriosus are determined primarily by the resistance to flow through the abnormal communication. In ductus arteriosus this will depend on the length and the diameter of the channel; other things being equal, the longer the vessel the higher the resistance. For convenience, a ductus with a high resistance to

flow may be termed "small" and one with a low resistance to flow may be termed "wide." The small ductus is the *classic patent ductus arteriosus*. In this type, the pressures in the aorta and pulmonary arteries differ significantly. Since the aortic pressure is constantly higher than the pulmonary pressure, a left-to-right shunt is present throughout the cardiac cycle (Figure VI-126). In spite of large volumes of flow, the pressure in the pulmonary vascular bed remains normal (Courmand, 1947; Dexter *et al.*, 1947). The continuous flow is responsible for a continuous murmur, the so-called *machinery or Gibson murmur* (Gibson, 1900), and for a continuous thrill. Cyanosis is absent. In the roentgenogram the pulmonary arterial segment and the "aortic knot" may each be prominent (Figure VI-127). Both by electrocardiography and roentgenography, the left ventricle may appear either normal or enlarged (Keats and Stenbach, 1955). A high systemic arterial pulse pressure may be present in some cases as an expression of "runoff" from the aorta. With surgical closure of the ductus, the aortic diastolic pressure rises and the pulse pressure falls (Taylor *et al.*, 1950). Body growth may be retarded, and this deficiency may persist even after surgical closure (Engle *et al.*, 1958).

The functional features of a *wide patent ductus arteriosus* are similar to those of large ven-

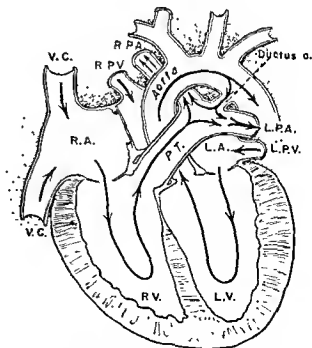


Figure VI-126. The circulation in patent ductus arteriosus of the small or classic variety.



Figure VI-127. Roentgenogram of the thorax in a boy aged 11 years with classic patent ductus arteriosus. Note characteristic prominence of the shadow of the pulmonary trunk.

tricular septal defect. Since there is no significant obstruction at the ductus, the pulmonary arterial and systemic arterial pressures are at similar levels. Assuming a constant systemic vascular resistance, the direction and volume of the shunt will depend on the pulmonary vascular resistance. In the young, the pulmonary vascular resistance is relatively low and, characteristically, the left-to-right shunt is large (Figure VI-128a).

During the first 6 months of life, a large shunt may produce major symptoms and even death. The hazard to infants with patent ductus arteriosus is now generally recognized (Mustard, 1951; Dammann and Sell, 1952; Ziegler, 1952; Adams *et al.*, 1953; Ferencz *et al.*, 1954; Lyon and Kaplan, 1954; Ash and Fischer, 1955). If infants with a wide ductus arteriosus survive the critical first 6 months or first year of life, the situation becomes relatively stable, either because the left ventricle tolerates the left-to-right shunt or because the volume of shunted blood is relatively lowered by an increase in pulmonary resistance.

Because of organic lesions described in patients with wide patent ductus arteriosus, the pulmonary vascular resistance ultimately rises to levels in the range of systemic resistance. A right-to-left shunt may then appear and the pulmonary flow falls (Figure VI-128b); this has often been called the stage of "reversing ductus arteriosus." A number of reports have appeared dealing with

the clinical and functional or with the pathologic features of this phase of wide patent ductus arteriosus (Burchell, 1948; Johnson *et al.*, 1950; Myers *et al.*, 1951; Bothwell *et al.*, 1952; Broustet *et al.*, 1952; Burchell *et al.*, 1953; Dammann *et al.*, 1953; Hultgren *et al.*, 1953; Smith, 1954; Yu *et al.*, 1954; Anderson and Coles, 1955; Harris, 1955; Shepherd *et al.*, 1955).

When patent ductus arteriosus with pulmonary hypertension is associated with only a left-to-right shunt, cyanosis is absent. When a right-to-left shunt appears, cyanosis may be apparent in the left upper and both lower extremities. The presence of "differential" cyanosis and of a lower oxygen saturation in the femoral arterial blood than in the right radial artery, are important points in distinguishing patent ductus arteriosus from other conditions in which a right-to-left shunt occurs within the heart, as in ventricular septal defect (Burchell *et al.*, 1953).

The clinical picture in wide patent ductus arteriosus is varied and, as in large ventricular septal defect, depends on the level of pulmonary vascular resistance. It lacks the machinery murmur which is so characteristic of classic or small patent ductus arteriosus. Usually a machinery murmur is not heard in infants with patent ductus arteriosus. In some cases the murmur has appeared after being absent (Holman *et al.*, 1953). This supports the concept that all patients with patent ductus arteriosus start life with pulmonary hypertension. Some patients (probably the majority) acquire the characteristics of a small ductus only after infancy; they also acquire a differential in pressure between the aorta and pulmonary arteries. Other patients throughout life maintain pulmonary hypertension and present clinical features like those of patients with large ventricular septal defects or other communications between the ventricles (Ferencz *et al.*, 1954) or aorticopulmonary septal defect (Adams *et al.*, 1952).

All patients with patent ductus arteriosus and pulmonary hypertension have *electrocardiographic evidence* of right ventricular hypertrophy. Left ventricular hypertrophy is associated with a large left-to-right shunt. In the latter event, the left atrial pressure may be elevated until the shunt is obliterated (Oustrières *et al.*, 1956). In infants, *roentgenographic examination* reveals nonspecific cardiac enlargement and signs of pulmonary congestion. In older patients, prominence of the shadow of the pulmonary trunk is a classic sign.

The diagnosis may be strongly suspected if cardiac catheterization reveals significantly higher saturation of oxygen in the preliminary arterial blood compared with blood from the right ventricle. This finding, usually indicative of patent ductus arteriosus because of its relative frequency, does not rule out an aorticopulmonary septal defect or other rare communication between the aorta and pulmonary trunk. Identification of the position of the catheter when it has passed through the defect tends to establish an absolute diagnosis (Adams *et al.*, 1952). Aortography likewise may readily establish the position of the communication. It is important to recognize that ventricular septal defect may be associated with patent ductus arteriosus, in these circumstances, it may be difficult to identify the presence of both defects by cardiac catheterization. The tendency is to identify the proximal defect on the basis of oxygen determinations, while the patent ductus may remain undetected unless the catheter enters this vessel (Bowers *et al.*, 1955).

COMPLICATIONS AND PROGNOSIS

Formerly discussions of the prognosis and complications in patent ductus arteriosus dealt mainly with patients who survived infancy. This is a restricted view because patent ductus arteriosus of the wide type may cause death during infancy from pulmonary edema as a complication of large left-to-right shunt. Recognition of this fact, and adoption of

early appropriate surgical therapy, has enabled many infants to survive.

Death from patent ductus arteriosus before the age of 3 months is probably uncommon. Heath and associates (1958b) observed 2 infants, each 2 days old at the time of death from pulmonary edema. The pulmonary arterial vessels had unusually thin walls. The pulmonary edema was attributed to left ventricular failure from a large left-to-right shunt through a patent ductus arteriosus.

Bullock and associates (1939) have reviewed the literature pertaining to complications of patent ductus arteriosus in patients who were 3 years of age or older at the time of death and who, at necropsy, had no significant anomaly associated with the patent ductus. They studied 80 such cases, 76 of which were taken from the literature. By the age of 14 years, 14 per cent of the group had died of their malformation; at 30 years of age, half of the patients had died, and by the age of 40 years, 71 per cent had died because of patent ductus arteriosus. Two of the patients in this study lived to the age of 66 years. The two leading causes of death were congestive cardiac failure and bacterial endarteritis.

Bacterial endarteritis in patent ductus is uncommon during the first decade (Schlaepfer, 1926, Gilchrist, 1945). The occurrence of bacterial endarteritis is probably limited to cases of the classic variety of ductus. In these, the site of trauma by the jetlike stream impinging on the



Figure VI-128. Roentgenograms of the thorax in 2 patients with patent ductus arteriosus and pulmonary hypertension. *a*. A large left-to-right shunt from which the patient died at the age of 3 months is featured by the evidence of congestion in the pulmonary fields. *b*. A right-to-left shunt with marked prominence of the large pulmonary vessels but no evidence of pulmonary congestion, an expression of the fact that pulmonary flow is not increased in this stage of the disease. The patient was 45 years old.



Figure VI-129. Pulmonary trunk and patent ductus, from a 13-year-old girl with bacterial endarteritis of the pulmonary trunk. The focus of infection (point of arrow) lies opposite the pulmonary end of the patent ductus arteriosus (D) P indicates pulmonary valve, A, aorta. Specimen submitted to the author by Dr. James H. Peers

pulmonary artery serves as a focus of predilection for infection (Figure VI-129). The ductus itself may become infected, and the infection may spread to the pulmonary arterial system with resulting pulmonary infarction. Uncommonly, emboli also may be carried into the systemic vessels. In fatal cases bacterial endocarditis of the aortic and mitral valves is common.

Jager (1940) reviewed 35 fatal cases of *septic thrombosis* of a patent ductus; he found the valves involved in 5 only. The tricuspid valve is least commonly affected. Involvement of the aortic and mitral valves probably results from seeding of the pulmonary blood with bacteria which are carried by the pulmonary veins to the left side of the heart. Although ligation of an infected ductus arteriosus is usually attended by good results, recovery may be jeopardized by secondary involvement of the cardiac valves (Touroff and Vesell, 1940; Touroff, 1943). Since the infecting organism is a *Streptococcus mitis* that is sensitive to penicillin, it is reasonable to expect that secondary valvular involvement will be less serious than it was prior to the introduction of antibiotic therapy. In the series of Bullock and associates, 42 (53 per cent) of 80 patients

died of the bacterial complication, while 18 (23 per cent) died of congestive cardiac failure. Five patients (6 per cent) died either from rupture of the ductus or from left ventricular failure. In 4 patients, death seemed to have been caused by a combination of effects of the patent ductus arteriosus and some other condition. The authors found that 69 (86 per cent) of the 80 patients died as a result of the patent ductus arteriosus.

Keys and Shapiro (1943) made a study of 60 (14 male and 46 female) patients who were 17 years of age or older at the time of death. The average age at death was 36.3 years; the oldest patient was 66 years. They estimated that in patent ductus arteriosus the *life expectancy* was reduced 23 years in men and 28 years in women. Approximately 4 of 5 patients died as a result of the malformation, 40 per cent from bacterial endarteritis and nearly 30 per cent from congestive cardiac failure. Ten patients had a pulmonary arterial aneurysm and 2 of them died from rupture of the aneurysm.

Rupture of a patent ductus arteriosus, in the absence of an aneurysm, is uncommon. Bronson and Sutherland (1918) mentioned that one of Roeder's patients, a female infant aged 3 days, died of rupture of a dissecting aneurysm of the ductus arteriosus. Another patient of Roeder, a male infant aged 2 days, died of rupture of a *fusiform aneurysm* of the ductus arteriosus.

Bland thrombosis of the ductus is uncommon, it is more likely to be encountered in the newborn period (Jager, 1940). According to Wells (1908), Rauchfuss observed thrombosis 12 times in 1400 necropsies on infants. Earlier workers had incorrectly explained that normal closure of the ductus arteriosus was accomplished by organization of a ductal thrombus. In the newborn period, thrombosis of the ductus arteriosus is usually an incidental finding. Pinniger (1949) reported the occurrence of a fusiform aneurysm of the ductus arteriosus containing an infected thrombus, in an infant aged 18 days who had had a staphylococcal abscess of the arm. The necropsy also showed pulmonary abscesses. Jager's patient, a woman of 55, had a bland thrombus in a patent ductus arteriosus, and died of intestinal infarction which resulted from embolism to the superior mesenteric artery.

Cardiac enlargement may recede after ligation of a patent ductus arteriosus (Gross, 1947). but in one instance (Dry *et al.*, 1948) sudden death from failure of the enlarged heart occurred

about 4½ years after a patent ductus had been ligated.

Aneurysm of the pulmonary arteries may result from acquired disease, such as syphilis or from congenital malformations in which an associated arteriovenous shunt or pulmonary hypertension represents an important underlying factor. The most common malformation is patent ductus arteriosus which is found in about a fifth of the cases of pulmonary aneurysm (Boyd and McGavack, 1939; Deterling and Clagett, 1947). The aneurysm may be either saccular or fusiform, and involves the pulmonary trunk more commonly than either of the major arteries. Occasionally it is mycotic and represents a complication of bacterial endarteritis, as in the second case of D'Aunoy and von Haam (1934).

SURGICAL THERAPY

Munro (1907) suggested surgical closure of the patent ductus arteriosus. Graybiel and associates (1938) unsuccessfully attempted obliteration of an infected patent ductus arteriosus. The first successful surgical closure was performed by Gross and Hubbard in 1938 and reported in 1939. Today surgical obliteration of patent ductus arteriosus is performed (Gross, 1952) for patients who do not have pulmonary hypertension and for those with pulmonary hypertension and a predominating left-to-right shunt (Anderson *et al.*, 1956; Ellis *et al.*, 1956). Many reports indicate the hazard of obliteration of the ductus in patients who have a predominant right-to-left shunt because of the high and fixed pulmonary vascular resistance resulting from organic occlusive lesions in the pulmonary arterial tree.

Aneurysm of Ductus Arteriosus

Aneurysm of the ductus arteriosus is rare and usually causes no functional disturbances. The usual picture is illustrated in Figure VI-130. The pulmonary end of the ductus is closed while the aortic end is patent and aneurysmal. Superficially such a lesion may appear to be an aortic aneurysm (Altschule, 1937). Histologically the wall of the aneurysm is composed of ductal rather than aortic tissue. Since a thrombus may form in the aneurysm, peripheral arterial embolism is a

potential complication. Thrombosis of fusiform aneurysms of patent ductus arteriosus has been discussed under complications of patent ductus arteriosus.

Graham (1940) reported 2 cases of exceptionally large aneurysms of the ductus arteriosus which gave the clinical impression of a mediastinal neoplasm.

Absence of Ductus Arteriosus; Right-Sided Ductus; Double Ductus

In the absence of the ductus arteriosus, the two circulations mix either in a common ventricle or in a persistent truncus arteriosus, or the pulmonary artery communicates with the aorta. The reason for the absence of the ductus arteriosus under these circumstances is understood if one reflects on the fate of that part of the right sixth aortic arch beyond the point of origin of the right pulmonary artery. This portion of the right sixth aortic arch is the right ductus arteriosus. Normally in the embryo, the blood leaving the heart is directed toward the left. This is accompanied by retention of the left-sided ductus while the right ductus undergoes progressive atrophy,



Figure VI-130. Aneurysm of the ductus arteriosus in a man aged 67 years. The pulmonary end of the ductus arteriosus is closed, while the aortic end is patent and dilated to aneurysmal proportions. A thrombus is contained in the aneurysm. An. indicates aneurysm; Lig. A., pulmonary end of closed ductus arteriosus; L.P.A., left pulmonary artery.

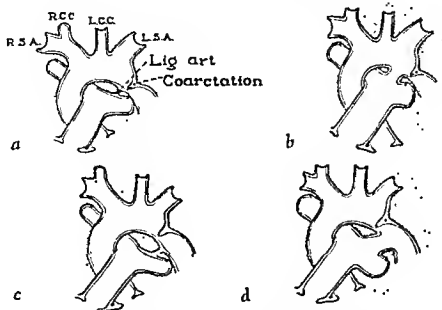


Figure VI-131. Coarctation of aorta. *a*, Distal to ductus arteriosus. Ductus is closed. *b*, Distal to ductus arteriosus. Ductus is patent. *c*, Proximal to ductus arteriosus. Ductus is closed. *d*, Proximal to ductus arteriosus. Ductus is patent. RSA and LSA = right and left subclavian arteries; RCC and LCC = right and left common carotid arteries. (From Clagett and associates, 1954. Reproduced with permission of the authors and *Surgery, Gynecology & Obstetrics*.)

so that by the time the fetus reaches maturity no vestige of it remains.

In the normal fetus the left-sided ductus serves as an overflow valve. Only a portion of the blood that leaves the right ventricle is received by the pulmonary arteries, the remainder flows through the ductus into the descending aorta. In conditions such as cor triloculare biatriatum, persistent truncus arteriosus, and anatomic tetralogy of Fallot, other "overflow valvular" mechanisms exist, depending on the malformation. In each of these conditions, the aorta is already in communication with both ventricles and the amount of blood which flows through the ductus during fetal life may be minimal, so that the ductus of the right side disappears and, sometimes, also that of the left side.

One should be skeptical of claims of absence of the ductus arteriosus in patients with normally developed cardiovascular systems, since it is unlikely that absence of the ductus would allow a fetus to attain normal development. Ordinarily such a report means that the examiner has overlooked an unusually delicate left ligamentum arteriosum or an existing right-sided ductus arteriosus. From a review of the fetal circulation (Chapter II), it is evident that, in the fetus with

normally formed ventricular and truncocoanal septa, the ductus arteriosus is an important overflow channel for blood leaving the right ventricle. While a fetus with intact ventricular and truncocoanal septa could survive absence of the ductus, this would require the shunting of a considerable amount of blood through the foramen ovale into the left side of the heart.

In the anatomic tetralogy of Fallot with right aortic arch, the ductus may be a left-sided structure and insert into the left innominate or left subclavian artery instead of into the aorta. Such an arrangement in the fetus does not allow the ductus to function normally, since the systemic connection of the ductus is not with the descending aorta. Any blood passing through the ductus would find its way either to the head or to the left upper extremity. This, however, should not cause embarrassment to the fetal circulation since in the tetralogy of Fallot the aorta communicates with the right ventricle and, therefore, an adequate and direct channel exists for right ventricular blood to enter the aorta and reach the placenta.

The subjects of right ductus arteriosus and double ductus arteriosus will be discussed under formation of Vascular Rings (page 464).

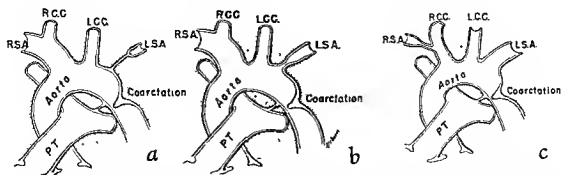


Figure VI-132. Coarctation of aorta distal to obliterated ductus arteriosus with anomalies of subclavian arteries. *a.* Atresia of left subclavian arterial origin. *b.* Stenosis of left subclavian arterial origin. *c.* Stenosis of right subclavian arterial origin. (From Clagett and associates, 1954. Reproduced with permission of the authors and Surgery, Gynecology & Obstetrics.)

COARCTATION OF AORTA

In coarctation of the aorta, the aortic lumen either in the arch or just beyond is significantly narrowed on a congenital basis. Goodson (1937) encountered, in more than 77,000 necropsies taken from several reports, 55 examples of aortic coarctation.

Classification

The classification commonly used in the past was that of Bonnet (1903) which consists of the infantile and the adult types of coarctation. In the infantile type, the coarctation lies proximal to the ductus arteriosus and usually distal to the left subclavian artery. In the adult type, the narrow zone lies either at the level of the aortic insertion of the ductus or immediately distal to it. This classification is not adequate because it does not take into account cases in which the coarctation lies in an unusual location or is associated with a patent ductus arteriosus or with lesions of the subclavian arteries.

The following classification considers the position and state of the ductus and of the branches of the aortic arch. The basic arrangements are those which characterize Groups I and II.

Group I. Coarctation distal to ductus arteriosus

- A. With closed ductus (Figure VI-131*a*)
- B. With patent ductus (Figure VI-131*b*)

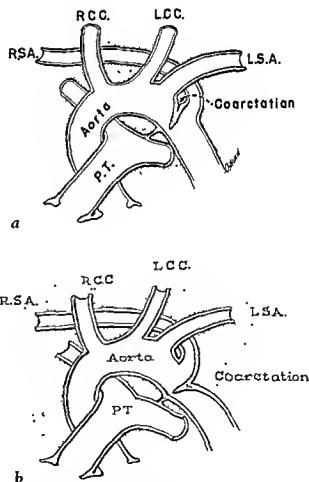


Figure VI-133. Coarctation of aorta beyond obliterated ductus arteriosus with anomalous origin of right subclavian arteries. *a.* Anomalous origin of right subclavian artery distal to coarctation. (From Clagett and associates, 1954. Reproduced with permission of the authors and Surgery, Gynecology & Obstetrics.) *b.* Anomalous origin of right subclavian artery proximal to coarctation.

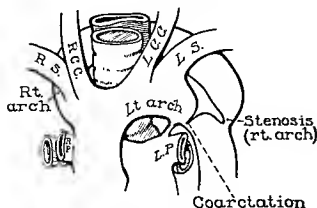


Figure VI-134. Double aortic arch with coarctation of left arch and stenosis of right arch. Case of Dry and associates (1953). (Reproduced with permission of the authors and *Diseases of the Chest*.)

Group II. Coarctation proximal to ductus arteriosus

- A. With closed ductus (Figure VI-131c)
- B. With patent ductus (Figure VI-131d)

Group III. Coarctation with anomalies of subclavian arteries or aortic arches

- A. Atresia or stenosis of left subclavian artery (Figure VI-132a and b; Woltman and Shelden, 1927; Bedford, quoted by Weber and Knop, 1929, Schwartz and Greene, 1942, Gerbode and Bourne, 1951; O'Sullivan, 1953)
- B. Stenosis of right subclavian artery (Figure VI-132c, Love and Holms, 1939)
- C. Anomalous origin of right subclavian artery
 1. Distal to coarctation (Figure VI-133a; Favcett, Case 12, 1905; Stephens, quoted by Gross, 1950, Sealy, 1951, Kroeker *et al.*, 1954)
 2. Proximal to coarctation (Figure VI-133b; Alcott *et al.*, 1956)
- D. Double aortic arch with stenosis of right and coarctation of left arch (Figure VI-134; Dry *et al.*, 1953)

Group IV. Coarctation in unusual locations

- A. Proximal to left subclavian artery (Figure VI-135)

1. With normal branches (Parker and Dry, 1938; Bagley and Holonbek, 1940; Bing *et al.*, 1948; Balin *et al.*, 1954; Edwards, 1954)
2. With anomalous origin of right subclavian artery (McGregor and Medalie, 1952; Vakil, 1953)
- B. Multiple sites (Benkowitz and Hunter, 1937; Efskind and Sanderud, 1955)
- C. Lower thoracic; abdominal (Bahnon *et al.*, 1949, Kondo *et al.*, 1950; Goldzieher *et al.*, 1951; Fisher and Corcoran, 1952; Patel and Facquet, 1953)

Pathologic Anatomy of Aorta and Heart

The usual location of coarctation of the aorta is opposite or just distal to the aortic insertion of the ligamentum arteriosum; sometimes it is somewhat proximal to that point. Externally, the aorta tends to have a constant appearance. Corresponding to the zone of luminal narrowing, there is a concavity of the outer contour of the vessel which involves the cephalic, ventral and dorsal aspects. Thus, the external concavity involves all walls except the caudal, into which the ligamentum arteriosum inserts. The caudal wall may be regular or distorted convexly (Figure VI-136a and b).

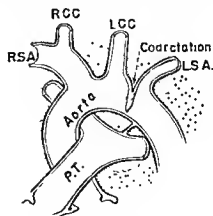


Figure VI-135. Coarctation in an unusual location lying between the origins of the left common carotid (L.C.C.) and left subclavian arteries (L.S.A.). (From Clagett and associates, 1954. Reproduced with permission of the authors and *Surgery, Gynecology & Obstetrics*.)

While the zone of greatest narrowing is frequently short and clearly defined, the diameter of the aorta leading to it tapers gradually. At times, however, the zone of narrowing may run for a distance of 1 cm. or more. Proceeding distally from the coarctation the aorta dilates gradually. The region of the coarctation thus has the configuration that would be made by placing two equal cones in a longitudinal plane with their apices directed against each other. On examination of the interior of the aorta, the lumen at the zone of coarctation is considerably narrower than is indicated from the external diameter. At this zone, the lumen is further narrowed by a diaphragmatic structure and is represented by a small opening in the diaphragm. The narrowed lumen lies toward the lower wall of the aortic arch.

Based on the size of the lumen at the level of the coarctation, Reifstein and associates (1947) classified the luminal narrowing as moderate when its diameter was 5 mm. or more, and as extreme when less than 5 mm. Judging from 104 cases reviewed by them and from 200 reviewed by Abbott (1928), in about one-fourth of the cases the narrowing of the lumen is moderate,

in about one-half, extreme; and in about one-fourth, no lumen is apparent. In the specimens which are removed as part of the operation for coarctation, the lumen is rarely more than 2 mm. in diameter. Though at times it has been said that no lumen is present, microscopic examination nearly always reveals a lumen, however tiny.

A fallacy frequently encountered in descriptions of the narrowed portion of the aorta is that the aorta appears as if it had a ligature placed around it. According to Craigie (1841), Paris published the first case in 1791 and Graham, the second case in 1814. Graham described the narrowing of the aorta as having an appearance exactly as though a ligature had been tied tightly around the aorta. In the ninth case which Craigie reviewed, that of Nixon, the patient was a young physician, aged 27 years.

The gross appearance is readily correlated with the microscopic features of coarctation. We have had the opportunity to make a microscopic study of an adequate number of segments of aorta with coarctation that have been surgically removed. Microscopically the basis for the aortic narrowing is a peculiar deformity and thickening of the aortic media (Edwards *et al.*, 1948a) in the cephalic, ventral and dorsal portions of the aortic wall. The thickened area projects into the lumen and makes it narrow and eccentric. In longi-

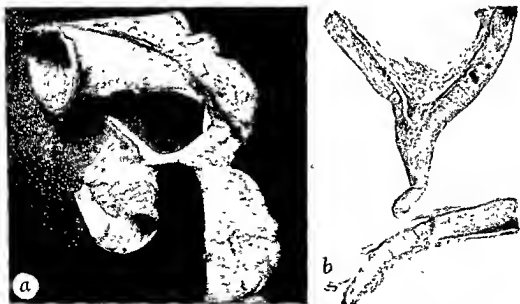


Figure VI-136. *a.* Coarctation of the aorta beyond the ligamentum arteriosum. The superior surface of the aorta shows characteristic deformity. From a man 31 years of age. *b.* Photomicrograph of a segment of the aorta removed surgically by Dr. O. T. Clagett because of coarctation. The aorta is sectioned longitudinally. The proximal portion is to the right, the distal to the left. While the inferior wall is regular in outline, the superior wall shows characteristic infolding of the media, producing an eccentric lumen of microscopic size. From a woman 30 years old. (El-GC, X4.)



Figure VI-137. *a*. From the aorta at the level of coarctation. Section prepared like specimen illustrated in Figure VI-136. The proximal portion is to the left, the distal to the right. The ligamentum arteriosum inserts into the inferior wall of the aorta proximal to the coarctation. The superior wall of the aorta shows characteristic infolding of the media, producing a narrow lumen. Overlying the medial curtain is a triangular mass of connective tissue representing secondary intimal thickening (El-VG, X 4½.) (From Edwards *et al.*, 1948a.) *b*. A longitudinal section through the isthmus of the aorta in the region of the ductus arteriosus, from a male infant who died at the age of 38 days. Beyond the isthmus and opposite the entrance of the ductus arteriosus, the aorta shows a characteristic curtain-like deformity of the media causing narrowing of the aortic lumen. (El-VG, X 6.)

tudinal sections the localized thickening of the media appears as a curtain (Figures VI-136*b* and VI-137*a* and *b*). The medial thickening is seen in cases of coarctation at all ages including infancy (Figure VI-137*b*).

Specimens from adolescents and adults often have, in addition, thickening of the intima at the zone of aortic narrowing. The intimal change is particularly prominent over the curtain of thickened media; in longitudinal sections it frequently has a triangular shape, the base being attached to the thickened media and the apex directed toward the opposite wall (Figure VI-137*a*). It is avascular and is composed largely of collagen laid down in concentric layers. Varying amounts of elastic tissue are present, particularly in the deeper portions of the tissue. Occasional smooth muscle cells are present. Since the intimal thick-

ening at the zone of luminal narrowing is minimal or absent in infants (Figure VI-137*b*), it is interpreted as developing after infancy. Moreover, its laminated structure and the presence of most of the elastic tissue in its deeper portions support the concept that localized intimal thickening develops progressively. Probably as a result of the constant force applied by the blood in the aorta proximal to the coarctation, the intimal tissue protrudes like a nipple into the aortic lumen distal to the coarctation (Figure VI-138*a*). This feature is comparable to the protrusion of the pulmonary end of a patent ductus into the lumen of the left pulmonary artery. The nipple-like protrusion of the margins of the opening in the diaphragm is one of the characteristics which distinguishes the proximal from the distal end of a segment of aorta with coarctation.

The diaphragmatic membrane at the site of coarctation, as seen in adolescents and adults, is composed basically of the localized medial thickening, the superimposed new intimal tissue may further decrease the diameter of the aortic lumen to some degree.

Distal to the coarctation the aortic wall is thin but the medial elements seem normal on microscopic examination. While the descending thoracic aorta is often of normal caliber, the abdominal aorta characteristically is narrow. Beyond the origin of the renal arteries, the diameter of the aorta frequently is hardly more than 1 cm. In the thoracic portion are seen wide ostia of the intercostal arteries. This change is particularly noticeable in the case of the upper 5 to 7 pairs of aortic intercostal arteries.

The portion of the aorta lying distal to the coarctation may show a *localized lesion* characterized by a corrugated patch which rises above the intimal surface (Figure VI-138*b*). Microscopically, such a lesion consists of localized fibrous intimal thickening, beneath which there may be distortion of medial architecture (Figure VI-138*c*). The lesion appears to result from trauma by a jet of blood striking the wall after passing through the zone of aortic narrowing. The jet lesion is significant for several reasons. (1) It may lie within that part of the aorta which is anastomosed during the operation for the relief of the coarctation. The avascular fibrous intima, if incorporated in the suture line, might then constitute a foreign body and prevent adequate healing at the site of the surgical anastomosis. (2) Since there may be loss of elastic tissue in the media beneath the jet lesion,

it could be conjectured that a saccular aneurysm might develop in this zone. It is conceivable that the jet lesion may also serve as the focus for the origin of a dissecting aneurysm below the level of the coarctation, a complication occasionally observed. (3) It may represent the point of origin of bacterial aortitis which characteristically starts just beyond the level of the coarctation.

A rare occurrence is *narrowing of the lower thoracic portion of the aorta or of the abdominal aorta*. While lesions in this area are commonly called coarctation, they differ from the picture of obstruction in the general region of the junction of the arch and the descending aorta. Narrowing in the lower thoracic or in the abdominal portions of the aorta usually occurs over a moderate distance, with uniform tapering of the aorta toward the narrowest point.

The peculiar association of congenital *bicuspid aortic valve* with coarctation is unexplained. In Abbott's (1928) review of the so-called adult type of aortic coarctation, bicuspid aortic valve was present in 23.5 per cent of the cases. Benkowitz and Hunter (1937) reported that bicuspid aortic valve occurred in 25.3 per cent of the 75 cases of aortic coarctation that had been reported since Abbott's review. In the interval between the appearance of the paper by Benkowitz and Hunter and that by Lewis in 1945, bicuspid aortic valves were encountered in 37.5 per cent of the cases reported. Reifstein and associates (1947) stated that the finding of a bicuspid aortic valve has been reported in 42.7 per cent of the 104 cases of the so-called adult type of aortic coarctation reported since the time of Abbott's review. The apparently increasing incidence of bicuspid aortic valve in cases of coarctation may be attributed to the emphasis placed on the possible occurrence of this additional malformation by Abbott and later writers.

The heart is often enlarged in coarctation of the aorta. If the ductus arteriosus is closed, hypertrophy develops, either predominantly or exclusively in the left ventricle. This is explained in part by the occurrence of systolic and diastolic hypertension in the aorta proximal to the coarctation. Another cause of left ventricular hypertrophy is aortic valvular insufficiency in the presence of a bicuspid aortic valve.

Collateral Circulation

The clinical diagnosis of the usual type of

coarctation of the aorta depends in great measure on demonstrating evidence of collateral circulation. For this reason, this feature of coarctation of the aorta will be discussed in detail.

According to Craigie (1841), Paris in 1791 and Graham in 1814 reported on the extensive collateral circulation in this condition. In the diagram in Meckel's (1827) report, the artist's portrayal of the erosions of the superior aspects of the ribs by the dilated intercostal arteries is probably inaccurate. White (1885) gave an accurate account of the collateral circulation, and more data were added by King (1926), Abbott (1928), Blackford (1928), Love and Holms (1939) and Bramwell and Jones (1941). Rosler (1928) and Railsback and Dock (1929) reported that the defects of the ribs caused by the enlarged intercostal arteries could be demonstrated roentgenographically and that this sign could be used in establishing the clinical diagnosis of coarctation. Batchelder and Williams

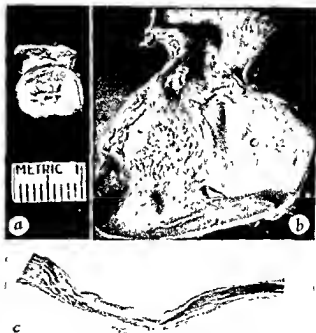


Figure VI-138. *a*. The distal end of a segment of aorta removed surgically by Dr. O. T. Clagett because of coarctation. The lumen is toward the inferior wall and the intima protrudes nipple-like into the lumen of the distal aorta. From a female patient 19 years old. *b*. The aorta from a man 29 years of age showing coarctation. Immediately inferior to the coarctation, there is a jet lesion characterized by a corrugated intimal surface. See *c* for photomicrograph. *c*. Photomicrograph of section through the jet lesion shown in *b*. The media is interrupted beneath the irregular intima. (El-G. X 4.)

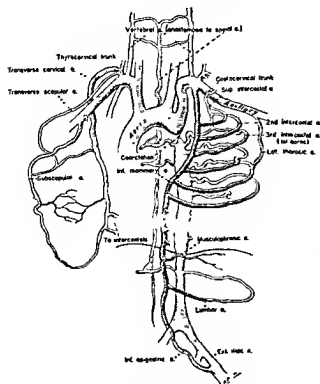


Figure VI-139. The collateral circulation in coarctation of the aorta. (From Edwards *et al.*, 1948b.)

(1948) observed costal notching in a patient with the tetralogy of Fallot.

On the basis of published accounts and our own experience (Edwards *et al.*, 1948b), we have prepared a diagram (Figure VI-139) of the collateral circulation in the usual type of coarctation of the aorta in which the ductus arteriosus is closed. The diagram shows that in the type of aortic coarctation represented, the *subclavian arteries*, through the communications of their branches, play the paramount role in carrying blood from the part of the aorta above the coarctation to the part below. The common carotid arteries are of minor importance in the collateral circulation in coarctation of the aorta, except in the presence of unusual forms of coarctation. The subclavian arteries may be greatly dilated, at times to aneurysmal proportions. Evidence of a pulsating and dilated left subclavian artery may be obtained on roentgenoscopy or by roentgenokymography (Cladmikoff, 1946; Stauffer and Rigler, 1950), and is particularly useful for the diagnosis of this condition when notching of the ribs is not demonstrable.

Ödman (1953) emphasized that enlargement of the internal mammary arteries, a common feature in coarctation of the aorta, may be demonstrated by angiocardiology and thoracic aortog-

raphy, and that pulsations of these arteries may even be visualized by roentgenoscopy.

The *intercostal arteries*, with the exception of the first two pairs, are most important anastomotic bridges. This is particularly true of the fourth through the seventh pairs of arteries (Lewis, 1933). These arteries act as bridges through their communication with the internal mammary, musculophrenic, superior epigastric, anterior spinal and lateral thoracic arteries and the descending branch of the transverse cervical artery, on the one hand, and the aorta below the level of the coarctation, on the other. Bramwell and Jones indicated that the *vessels about the scapula*, which communicate directly or indirectly with the intercostal arteries, far overshadow the communications of the intercostal arteries with the internal mammary artery and its terminal branches. On the other hand, Railsback and Dock, while cognizant of the communications of the intercostal arteries with the arteries of the scapula, stated that in their case the anterior communications of the intercostal arteries with the internal mammary arteries seemed to represent the important avenues of collateral circulation. The internal mammary arteries are consistently dilated and tortuous.

Pulsation of the dilated arteries related to the scapula is a frequent and a clinically valuable diagnostic sign (Walshe, 1873; Blackford, 1928; Campbell and Suzman, 1947). In an analysis of the clinical features in 96 cases of aortic coarctation, Christensen and Hines (1948) noted that evidence of a collateral supply had been sought in 74 patients, and found in 61 of these (82.4 per cent) on physical examination. This evidence was observed most frequently over the scapular and interscapular regions and less frequently in the supraclavicular regions. In these regions the collaterals may be felt to pulsate and, in some cases, *murmurs* may be heard over the arteries.

The intercostal arteries, by virtue of their function, become greatly dilated and tortuous. Dorsally in particular, the tortuosity produces pressure atrophy of the adjacent ribs. Sometimes this atrophy is represented by mere enlargement of the costal grooves of the ribs (Wolke, 1937; Figure VI-140a); at other times, by gross focal erosion of the substance of the rib (Figure VI-140b and c). Erosion represents an important diagnostic feature in coarctation of the aorta since the notches are readily recognized in *roentgenograms*. Contrary to the common statement that the lower margin of the rib is notched in coarcta-

tion, the notching occurs on the inferior and ventral aspect of the main body of the rib, at the point at which it joins that part of the rib which forms the wall of the costal groove (Ernstene and Robins, 1931). Since the inferior portion of the rib which forms the posterior wall of the costal groove is thin in comparison to the superior portion of the rib, it may be sufficiently penetrated by roentgen rays to become invisible in the roentgenogram. Under such conditions, the notching appears to involve the inferior margin of the rib. This picture, however, is an illusion produced by roentgen-ray penetration of the inferior portion of the rib. Crafoord and associates (1947) and Pugh (1948) have pointed out that when roentgenograms of the thorax of patients with coarctation of the aorta are examined carefully, one frequently can demonstrate a portion of the rib inferior to the portion that is notched; these roentgenographic changes correspond to anatomic changes (Figure VI-141). About one-fourth of the patients with coarctation of the aorta do not have roentgenologically demonstrable notching of the ribs (Pugh). The process of erosion of the ribs must be progressive, since most instances of absence of notching are encountered among children. Sometimes, however, notching is demonstrable in children, and sometimes it is not evident in adults. Brown (1939) stated that notching had been recorded earliest at 6 years of age, Blumenthal and Davis (1941), at 5 years; and Neuhauser (1946), in an infant 19 months of age.

The reason that the first two intercostal arteries do not play a large role in the collateral system is that they usually do not communicate with the aorta dorsally, as the other intercostal arteries do. Dorsally, the first two intercostal arteries communicate with the superior intercostal artery which in turn is in communication, either directly or through the costocervical trunk, with the subclavian artery of the same side. The superior intercostal artery may, however, serve a bridging function by its anastomosis with the third intercostal artery, at a point ventral to the site at which the latter vessel arises from the aorta as the first aortic intercostal artery.

The superior epigastric artery communicates prominently with the cephalic portion of the inferior epigastric artery. Through this channel a substantial amount of blood may be carried from the subclavian artery to the external iliac and femoral arteries. As judged from the width of this channel and from the narrow state of the lower part of the abdominal aorta, a considerable

amount of blood carried to the legs probably avoids the lower part of the aorta entirely. In spite of characteristic absence of pulses in the abdominal aorta and in the iliac and femoral arteries, the volume of blood flow to the legs is within normal limits (Wakim *et al.*, 1948).

The position and the communications of the anterior spinal artery are represented in Figure VI-139. This artery may serve as a collateral channel in coarctation of the aorta since it lies along the entire length of the spinal cord and so forms a continuous channel past the level of the aortic narrowing. By communications from the vertebral arteries in the cervical region, it receives blood derived from the subclavian arteries, which primarily comes from the aorta proximal to the level of stenosis. Furthermore, by its communications with the intercostal and lumbar arteries in the thoracic and lumbar regions, respectively, the anterior spinal artery may carry blood flowing into it from the vertebral arteries prox-

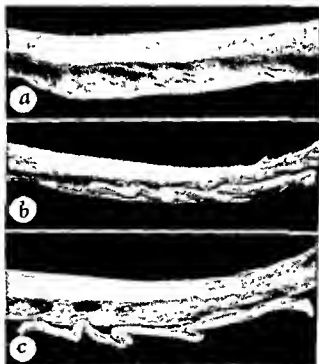


Figure VI-140. *a* A rib removed during operation for coarctation, showing irregularity of the contour and enlargement of the subcostal groove. From a woman aged 19 years whose aorta is illustrated in Figure VI-138*a*. *b*. Posterior portion of a rib in a man aged 19 years, with coarctation of the aorta. The intercostal artery is tortuous. (See *c*.) *c*. The intercostal artery illustrated in *b* has been removed; at the points of tortuosity of the artery, the rib is notched. The notches occur in the inferior aspect of the main body of the rib and in the adjacent portion forming the subcostal groove. The inferior margin of the rib is not notched. (Figures VI-138*b* and *c* from Edwards *et al.*, 1948*b*.)

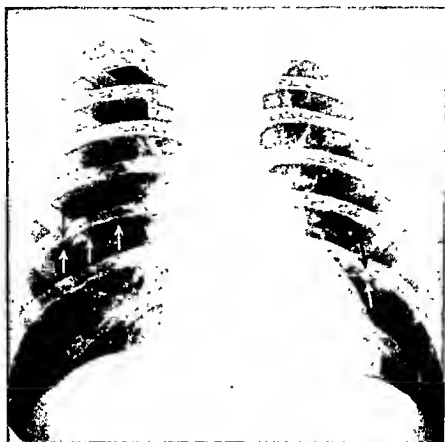


Figure VI-141. Roentgenogram of the thorax in a patient with coarctation of the aorta. The white arrows point to the inferior margins of the ribs. The black arrows point to the notching in the main body of the ribs. (From Fugh, 1948.)

imally toward the aorta distally. The role of the anterior spinal artery as a collateral channel has received relatively little attention in the past; in our experience (Edwards *et al.*, 1948b), this artery is often dilated and tortuous in aortic coarctation, particularly in the cervical and thoracic regions (Figure VI-142). Evidently, symptoms resulting from the dilated state of the anterior spinal artery are not common. Haberer's (1903) patient (quoted by Herxheimer, 1910, and Abbott, 1928) was reported to have transverse myelitis which resulted from compression of the spinal cord by the dilated spinal artery. However, the sudden onset of symptoms and the finding at necropsy of a thrombus in the artery suggest that the arterial occlusion had a greater influence in causing changes in the spinal cord than did the dilatation of the artery. Haberer mentioned a case of Brasch in which slowly developing paralysis resulted from compression of the spinal cord by a dilated and tortuous anterior spinal artery.

It is appropriate to indicate that the col-

lateral circulation characteristic of aortic coarctation begins during intra-uterine life. In the usual type of aortic coarctation, the coarctation lies distal to the aortic ostium of the ductus arteriosus, whether patent or closed. In the fetus, this anatomic arrangement would be incompatible with life unless collateral channels bypassed the coarctation. Evidence to support the opinion that collateral circulation is set up during the fetal life, in instances of coarctation lying distal to the ductus, is found in attainment of full maturity of the fetus. In coarctation lying proximal to the ductus, the fetus may develop fully in the absence of collateral circulation.

Functional Disturbances and Clinical Features

COARCTATION WITH CLOSED DUCTUS ARTERIOSUS

Brown and associates (1948) defined the func-

tional characteristics of coarctation of the aorta as follows: (1) The systolic and diastolic pressures in the upper extremities are elevated; (2) the systolic pressure of the lower extremities is normal or reduced, but the diastolic pressure is, as a rule, elevated, (3) the ratios of femoral to radial systolic pressure and of femoral to radial pulse pressure are below the range of similar ratios in normal persons; (4) the femoral pulse wave is delayed when compared with the time of onset of the radial pulse wave; and (5) the period between the onset and the peak of the femoral pulse is usually longer than that observed in normal persons. The basis for hypertension in coarctation of the aorta is not clear (Stewart *et al.*, 1944, Bing *et al.*, 1948). One theory holds that the hypertension is caused by the obstructing lesion in the aorta and by the relatively narrow state of the collateral bed; another belief attributes it to a generalized increase in peripheral resistance, possibly because of pressor substances eliminated by the kidneys resulting from lack of a normal pulsatile flow of blood (Scott and Bahnson, 1951).

The clinical manifestations vary. The majority of patients with coarctation of the aorta and closed ductus arteriosus do not manifest any symptoms in infancy. The symptoms in infancy (Kesson, 1948, Calodney and Carson, 1950, Olney and Stephens, 1950, Bahn *et al.*, 1951, Rogers *et al.*, 1952; Mustard *et al.*, 1955) are non-specific for chronic left ventricular failure. These include failure to take proper nourishment and to gain in weight. The roentgenogram shows non-specific cardiac enlargement. Hypertension may be demonstrated in the upper extremities while the femoral pulses are usually not palpable. The latter feature is probably the most important clinical sign distinguishing coarctation of the aorta from other causes of left ventricular failure in infancy. Notching of the ribs does not usually occur at this early period.

The differences in symptomatology among patients with coarctation of the aorta seem to depend on the position of the coarctation with respect to the ductus arteriosus (Bahn *et al.*, 1951). If the coarctation lies proximal to the ductus arteriosus, no stimulus is present in fetal life for the development of collateral vessels. When the ductus closes after birth, the entire left ventricular output is met by the obstructed aorta which has an inadequate collateral system. This may be responsible for hypertension. If the coarctation is distal to the ductus arteriosus, in all probability collateral channels develop during fetal

life if the fetus is to survive. In such patients after birth, the closure of the ductus arteriosus does not materially affect the circulation, since collateral pathways have already been established. It is probably this group of patients who live to later life before symptoms become apparent. Successful surgical correction of symptomatic aortic coarctation in infants has been accomplished (Lynxwiler *et al.*, 1951, Kirklin *et al.*, 1952; Sealy and Webb, 1953; Mustard *et al.*, 1955).

Patients with coarctation of the aorta and with a closed ductus arteriosus may remain asymptomatic until later life. A common early finding is hypertension with disparity in pressures between the upper and lower extremities. In the lower extremities and in the abdominal aorta, pulsations are either not evident or are considerably weaker than in the upper portion of the body. Other evidences of the coarctation pertain to demonstration of a collateral system. In some patients, the predominant clinical features may center about a complication.

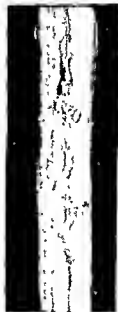


Figure VI-142. Lower cervical and upper thoracic portion of the spinal cord, from a man aged 19 years with coarctation of the aorta. One of the ribs of this patient is illustrated in Figures VI-138b and c. The anterior spinal artery is dilated and tortuous.

Campbell and Suzman (1947) reported that, among 15 patients with aortic coarctation, *aortic diastolic murmurs* were heard in 6. In 1 of these, the murmur was related to rheumatic endocarditis, in the other 5, to the coarctation. Christensen and Hines (1948) reported that 20 per cent of 96 patients with clinical aortic coarctation had diastolic cardiac murmurs, usually situated over the base of the heart. They indicated that while such a murmur can be caused by an incompetent bicuspid aortic valve, it might be the result of other conditions such as an associated patent ductus arteriosus, ventricular septal defect and bacterial or rheumatic endocarditis.

In a review of coarctation of the aorta, Campbell and Baylis (1956) found that about one-fourth of 130 patients had evidence of some degree of aortic insufficiency which they attributed to acquired calcific aortic valvular disease. Sloan and Cooley (1953) emphasized the value of *angiocardiology* or aortography in determining the position and nature of the coarctation. Bruwer and Pugh (1952) reported that, on postero-anterior roentgenographic examination, a notch in the left border of the descending aorta just above the level of the left pulmonary artery was seen in about a third of the patients with proved coarctation of the aorta. This notch, according to the authors, represented the narrowed segment of the aorta. In about 5 per cent of the cases studied, the roentgenogram showed no notching of the ribs but *did show the sign described*. Kinking of the aorta (so-called pseudo-coarctation) may yield a sign somewhat similar to the notching of the aorta in patients with true coarctation (Bruwer and Burchell, 1956).

DIFFERENCES IN BRACHIAL BLOOD PRESSURES

Significant differences in the blood pressure of the two arms exist in a small number of patients with coarctation of the aorta. Among 170 patients with coarctation, King (1937) noted that in 9, the brachial systolic blood pressure was normal on the left side and elevated on the right. In 4 of these cases, however, the brachial diastolic pressure was elevated on the left side. King added a tenth clinical case.

If the blood pressures in the two arms differ significantly, the collateral system (if present, as indicated by notching of the ribs) exists on the side with the higher blood pressure (Love and

Holms, 1939; Edwards, 1954). It was noted by Burchell and associates (1950), however, that costal notching at times may not be apparent on either side. Grishman and associates (1944) described the roentgenographic features in cases of aortic coarctation with absence of the left radial pulse. Rarely, as in a report by McGregor and Medalie (1952), blood pressures and pulses may not be obtained in any of the four extremities. In their case, the carotid arteries carried collateral blood to the circle of Willis, and from this position, blood was carried by way of the vertebral system to the portions of the body inferior to the site of the coarctation. The vascular changes found were aortic coarctation, located between the left common carotid and left subclavian arteries, and a right subclavian artery that arose distal to the coarctation.

COARCTATION OF LOWER THORACIC OR ABDOMINAL PORTIONS OF AORTA

Coarctation involving the lower thoracic or the abdominal aorta may be manifested by hypertension and absence of a readily demonstrable collateral system.

COARCTATION AND PATENT DUCTUS ARTERIOSUS

The clinical picture varies among patients having coarctation of the aorta and patent ductus arteriosus (Johnson *et al.*, 1951; Taylor *et al.*, 1950). Formerly it was thought that the variation depended on the position of the coarctation with respect to the patent ductus arteriosus (Edwards *et al.*, 1949). At present the author believes that the relative position of the two co-existing lesions is probably of little importance in patients surviving infancy, while the size of the *ductus arteriosus* is paramount. When the ductus arteriosus is relatively narrow, the clinical picture is that of coarctation with a well-developed collateral system and signs of classic patent ductus arteriosus. Patients with a wide ductus arteriosus present signs of pulmonary hypertension. They may also have manifestations of coarctation of the aorta, if the flow is from the aorta into the pulmonary artery and if the collateral system, bypassing the coarctation, is well developed. Among patients having a right-to-left shunt through the ductus arteriosus, it is less likely that a collateral system associated with the coarctation will be demonstrable (Haxton and Thomson, 1948; Leeds *et al.*, 1953). In these instances, significant differences in oxygen

saturation between the upper and lower portions of the body may be apparent. In such cases, the picture may be difficult to distinguish from so-called reversing ductus arteriosus without associated coarctation.

TURNER'S SYNDROME

About 10 per cent of persons with ovarian agenesis (as part of Turner's syndrome) also have coarctation of the aorta. Extensive reviews of this syndrome were made by Wilkins and Fleischmann (1944) and van Creveld and de Vaal (1949). Other outward signs of this developmental disturbance include webbing of the neck and increased carrying-angles at the elbows.

Complications and Prognosis

Coarctation of the aorta may occasionally allow a patient to reach a full span of life. The patient of Hayes and Stauffer (1949) was living at age 72 years. The malformation often produces death prematurely. Before complications develop, the patient frequently has no disability and may partake in arduous labor. Newman (1948) reported on 23 patients who had served in the British military forces. As a rule, in women with coarctation, cardiac compensation is maintained during pregnancy (Baber and Daley, 1947, review of 43 cases with pregnancy; Shanahan *et al.*, 1958).

Of 104 fatal cases of the so called adult type of coarctation, in which the ratio of males to females was 5:1, Reifenstein and associates (1947) found that 61 per cent of the patients who had survived infancy did not live beyond age 40. The average age at death was 35 years. Three-fourths of the patients died as a result of the malformation, the others from unrelated causes. The 4 common fatal complications are: left ventricular failure, bacterial endocarditis or aortitis, dissecting aneurysm of the aorta and rupture of an aneurysm of the circle of Willis. Left ventricular failure results either entirely or in part from the existing hypertension. Insufficiency of the bicuspid aortic valve may contribute to left ventricular failure. In Reifenstein's series 18 per cent of the patients died of congestive cardiac failure, the average age at death being 39.3 years.

Bacterial endocarditis usually develops upon a bicuspid aortic valve (Kellogg and Biskind, 1934; Wechsler and Gustafson, 1937; Hallock and Heibel, 1939) (Figure VI-143a). Bacterial endocarditis accounts for death in about a fifth of

the cases of aortic coarctation (Abbott, 1928; Blackford, 1928; Reifenstein *et al.*, 1947). Other foci of intravascular infection are less common. Reifenstein and associates reported bacterial aortitis involving the ascending aorta in 2 of 104



Figure VI-143. a. Bacterial endocarditis complicating a bicuspid aortic valve, from a man aged 25 years with coarctation of the aorta. b. The left ventricle and aorta, from a woman aged 34 years with aortic coarctation. Beyond the origin of the dilated left subclavian artery the aortic lumen narrows sharply and characteristically. In the ascending aorta, above a bicuspid aortic valve, there is a rent characteristic of dissecting aneurysm. Rupture of the aorta into the pericardial sac caused death. (From a case of the late Dr. Timothy Leary of Boston. Illustration reproduced with his permission.)

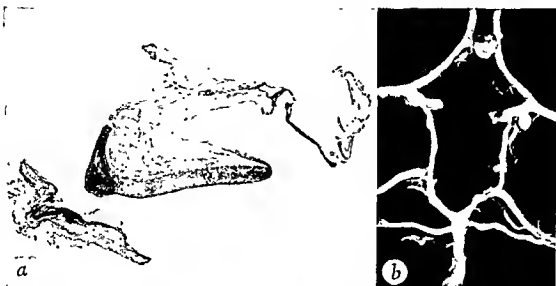


Figure VI-144. *a* Photomicrograph of a specimen of aorta removed surgically by Dr. O. T. Clagett for coarctation. The aorta has been oriented and sectioned like the aortas in Figures VI-136*b* and VI-137. The proximal portion of the aorta lies to the left. The aortic end of the ligamentum arteriosum blends with the lower surface of the aorta. Immediately distal to the ligamentum the superior wall of the aorta shows the characteristic medial deformity causing coarctation. An aneurysm involves the descending aorta and the mouth of an intercostal artery. (El-vG; X 4.) *b*. The circle of Willis, from a man aged 28 years with coarctation of the aorta. Two aneurysms, neither of which has ruptured, are present. (From Edwards et al., 1948a.)

cases and similar lesions just distal to the coarctation in 4 other cases.

Bauer and Iverson (1945) reported 2 cases without bacterial endocarditis but with *bacterial aortitis* and *mycotic aneurysm* originating just beyond the coarctation; in 1 instance the aortic aneurysm ruptured and in the other, a secondary mycotic aneurysm of the superior mesenteric artery ruptured. They found in the literature 10 other cases of primary bacterial aortitis complicating coarctation. The ages of the patients varied from 6 to 38 years, Koletsky's (1942) patient being the oldest. An aortic mycotic aneurysm, either proximal or distal to the coarctation, may be secondary to a complicating bacterial endocarditis.

Rupture of the aorta, other than as a result of localized bacterial infection, is also a common cause of death. The most frequent lesion in this group is *dissecting aneurysm* originating in the ascending aorta (Figure VI-143*b*). It causes death in about 17 per cent of cases of coarctation. Less often, fatal aortic dissecting aneurysm originates distal to the coarctation. Cases of aortic coarctation complicated by *dissecting aneurysms* have been reported by Binder (1919), Boyd and Werhlow (1937), Regester and Innes (1938), Black (1942), Lewis (1945) and Grieve

(1952). Usually the dissection starts in the ascending aorta or arch and terminates at the level of the coarctation, with rupture occurring into the pericardial sac.

Rupture of the aorta distal to the coarctation may occur in a mycotic aneurysm, a bland saccular aneurysm or a dissecting aneurysm (Balin et al., 1954). Mycotic aneurysms of the distal portion of the aorta may occur as a complication of bacterial endocarditis or may result from primary bacterial aortitis (France et al., 1950). Moragnes and associates (1942) found only 5 cases of rupture of the aorta distal to coarctation that had been reported. Their patient, a boy aged 11 years, had a saccular aneurysm just beyond the coarctation, which ruptured into the esophagus. Hecker's patient (1939), a man aged 62 years, had a dissecting aneurysm of the descending aorta. The patient of Zaslow and Krasnoff (1943), a man aged 25 years, had a fusiform aneurysm of the descending aorta which ruptured into the left pleural cavity. These authors suggested that eddy currents in the blood just distal to the coarctation may have caused gradual weakening of the aorta with formation of aneurysm. They expressed this opinion (which is probably correct), even though they found mucinous cysts in the media of the aorta. Rupture of the aorta through a jet

lesion was described by Bellet and Gelfand (1952). Blickman (1949) expressed the opinion that localized formation of bland aneurysm beyond the coarctation is the result of primary deficiency in the structure of the aorta rather than of localized trauma as postulated by Edwards and associates (1948a). An infected or a bland aneurysm may develop at the site of the aortic anastomosis after repair of coarctation (Blickman, 1949, Martin *et al.*, 1956). Clark and Koenig (1947) reported the roentgenologic and pathologic features of an unruptured bland saccular aneurysm of the descending aorta in a woman of 25. Halonen and Aho (1949) described 2 cases of aortic coarctation complicated by saccular aneurysm just beyond the constriction. One occurred in a woman aged 39 years; in the other patient, a man aged 20 years, the aneurysm ruptured.

Excision of an aneurysm of the descending aorta in patients with coarctation of the aorta has been reported by Alexander and Byron (1944) in a 19-year-old youth, and by Shumacker (1948) in a boy aged 8½ years. Dr. O. T. Clagett of the Mayo Clinic, excised an aneurysm (Figure VI-144a) from a 24-year-old woman, which was continuous with the aorta but seemed to arise from an intercostal artery.

Abbott noted *neurologic lesions* in 25 of the 200 cases which she reviewed. Twenty of these had an intracranial hemorrhage, mainly as a result of *rupture of an aneurysm of the circle of Willis* (Figure VI-144b). In 5 cases other types of neurologic lesions were observed, these included cerebral emboli and rarely involvement of the spinal cord, as in the cases of Haberer (1903) and of Christian and Noder (1954). Among 104 cases reviewed by Reifenshtein and associates, 13 patients had intracranial lesions, in 9 instances the brain was examined and a ruptured aneurysm of the circle of Willis was found in 5 (as in the cases of Davies and Fisher, 1943, and Wright, 1949). Two patients had a subarachnoid hemorrhage but an aneurysm was not found. One patient had lesions caused by cerebral atherosclerosis, and in 1 patient, embolism to the brain complicated an aneurysm of the aorta. These cases of cerebral complications of coarctation do not include those in which bacterial endocarditis was present.

The patient of Clark and Firminger (1949), a man aged 31 years, had complete heart block and Adams-Stokes syndrome associated with calcific stenosis of a bicuspid aortic valve. In the report of Moore and Dimond (1946), the Wolff-

Parkinson-White syndrome was observed in a boy aged 15 years with coarctation. The association was believed to be coincidental. Smith and Matthews (1955) emphasized that calcific stenosis may complicate congenital bicuspid aortic valve associated with coarctation of the aorta (Figure VI-145). Reifenshtein and associates reported that *calcification of bicuspid aortic valves* was present in 11 of 93 cases of coarctation of the aorta in which the pathologic descriptions were adequate. In some patients having aortic coarctation and obstruction at the aortic valve, it is impossible clinically to distinguish acquired calcific disease from coexisting congenital subaortic stenosis (Kroeker *et al.*, 1954). In patients with associated aortic or mitral valvular disease, resection of the coarctation may be followed by acute circulatory failure (Jacobson *et al.*, 1953).

Endocardial sclerosis of the left ventricle may be observed with coarctation of the aorta at necropsy in infants (Bahn *et al.*, 1951). It is uncertain whether this represents a secondary lesion or whether it is always an associated congenital anomaly, as suggested by Oppenheimer (1953). The author believes that in some instances the left ventricular endocardial sclerosis is secondary to the dilatation of left ventricular failure which is the result of the coarctation.

Necrotizing arteritis of the abdominal organs with infarction may follow repair of coarctation of the aorta (Lober and Lillehei, 1954; Perez-Alvarez and Oudkerk, 1955; Benson and Sealy, 1956).

DEVELOPMENTAL BASIS

The so-called skodaic hypothesis, fre-



Figure VI-145. Unopened aortic valve from above, showing a calcified stenotic congenitally bicuspid valve. From a man with coarctation of the aorta.

quently mentioned as the cause of coarctation of the aorta, was evidently first proposed by Craigie. It assumes that the coarctation is caused by an overgrowth into the aorta of the tissue that closes the ductus arteriosus.

Even without observations on the structural nature of the coarctation, there are sufficient objections to this hypothesis to make it untenable. For one thing, it does not explain cases of coarctation in which the aortic stricture lies some distance from the ligamentum arteriosum, nor does it explain the rare occurrence of coarctation at two sites (Benkowitz and Hunter, 1937; Efskind and Sanderud, 1955). Moreover, coarctation sometimes exists in the presence of a patent ductus arteriosus.

Pezzi and Agostoni (1928), on the basis of histologic studies, claimed that smooth muscle which causes the obliteration of the ductus arteri-

osus invades the wall of the aorta and encircles it. By its proliferation, the smooth muscle causes a beltlike constriction of the aorta. Bremer (1948), on the basis of studies on pig embryos, expressed the opinion that the so-called adult type of coarctation in human beings was caused by extension of ductal tissue into the aorta. Friedberg (1941) regarded coarctation as a developmental disturbance of the aorta itself. After studying reconstructions of the aorta and ligamentum arteriosum in coarctation, my associates and I believe that the tissue of the ductus arteriosus in coarctation of the aorta has the same relationship to the aorta as in normal persons. Though I must reject the skodaic hypothesis, I cannot offer an explanation for the cause of coarctation. Since coarctation is observed at birth, the condition should be regarded as a congenital malformation developing during intra-uterine life. Its occurrence in siblings (Moss, 1955) supports this view.

INTERRUPTION OF AORTIC ARCH

Interruption (complete interruption of continuity) of the aortic arch functionally resembles coarctation of the aorta but probably has a differential developmental basis. A patent ductus joins the descending aorta.

Kleinerman and associates (1958) reported that the literature contained reports of 21 cases. They observed 6 additional cases over a period of 10 years at the Cleveland City Hospital. Associated cardiac defects are common, the most important being ventricular septal defect. This malformation was present in 16 of the 18 cases reviewed. In an additional case, cor biloculare was present; and in 1 of the 18 cases reviewed, intracardiac defects were absent.

The position of the great vessels arising from the aortic arch varied with respect to the site of obliteration of the arch. Most often (in 7 instances reviewed by Kleinerman and associates), the left subclavian artery arose from the descend-

ing aorta just proximal to the junction of the descending aorta with the ductus arteriosus. In only 4 cases did the three branches of the arch arise in the normal sequence. Origin of both subclavian arteries from the descending aorta occurred 3 times. Hypoplasia of the ascending aorta is common and the aortic valve is bicuspid in about half the cases. Death during early infancy is the rule, probably because of the commonly associated serious intracardiac malformations combined with aortic obstruction.

In the case reported by Barger and associates (1954), the ascending aorta terminated by dividing into the two common carotid arteries. A ductus arteriosus was present on each side. The left subclavian artery arose from the descending aorta which joined the left ductus arteriosus while the right subclavian artery arose from the right ductus arteriosus and had no communication with any portion of the aorta.

VASCULAR RINGS

By common usage the term *vascular rings* refers to malformations of the aortic arch system which are responsible for interference with the function of the trachea and the esophagus. In this section, we shall discuss

these malformations as well as those that are developmentally related to them. In most but not all of the malformations to be covered, the cardiac development is normal and the ductus arteriosus also closes normally.

Nevertheless, the ductus arteriosus or the ligamentum arteriosum plays an important role in the development of the vascular rings. In particular, we shall discuss the position and attachments of the ductus arteriosus. Unless specifically stated, use of the term "ductus arteriosus" will imply a normally closing or closed ductus arteriosus.

Reviews of anatomic types of vascular rings are included in the papers of Grob (1949), Cross and Neuhauser (1951) and Edwards (1953). In offspring of rats deficient in vitamin A, Wilson and Warkany (1950) experimentally induced aortic anomalies similar to those in the human being.

Surgical division of vascular rings is designed to relieve compression of the esophagus or trachea or both. In most instances, dramatic relief of tracheal obstruction is obtained by the surgical procedure, but sometimes symptoms persist for months as a result of continuing deformity of the trachea (Carson and Goodfriend, 1949).

Rarely anomalous arteries arise from the descending thoracic or abdominal aorta to supply part of the pulmonary tissue. Sometimes the pulmonary tissue has a normal bronchial connection; in other instances, the part of the lung supplied by the anomalous artery is isolated. Anomalous arteries of this type do not fall into the category of vascular rings. (For review of the subject, see Findlay and Maier, 1951).

Many anatomic classifications have been offered for malformations of the aortic arches. Most classifications, however, do not include the malformations in which the ductus arteriosus or the ligamentum arteriosum is on the right side. It is difficult to supply a classification which is all-inclusive. Nevertheless, I have presented (Edwards, 1948a) a workable classification. For a comprehensive understanding of the malformations of the derivatives of the aortic arch system, it is desirable that the various forms bear some developmental relationship to each other. In this way, various malformations could be related to the aortic arch system portrayed in the standard Rathke diagram of the six pairs of aortic arches; and, by obliteration or disappearance of certain parts of this system, the various known forms could be derived and certain forms as yet undescribed could be anticipated.

The Rathke diagram has several shortcomings. The definitive aortic arch is portrayed as derived only from the primitive left fourth arch. Barry

(1951) has indicated that the origin of the arch of the aorta is more complex, important changes in the shape and relations of the arch occurring between the times portrayed by the diagram and the time of birth. Some of these changes are the result either of different rates of growth of the various parts of the system or of adaptation to the shape of other structures developing in the mediastinum. Another possible source of confusion is that, in the stages portrayed in the Rathke diagram, the subclavian artery lies caudad to the sixth aortic arch which is to form the ductus arteriosus but, by the time of birth, the subclavian artery lies in a position cephalad to the ductus arteriosus. It would, therefore, be preferable to use a pattern which retains those parts of the primitive aortic arch pattern that are necessary for an understanding of the subject and which at the same time has gone through the adjustments of growth and the shift of the subclavian artery to its definitive position cephalad to the ductus arteriosus. Therefore, I proposed using a malformation known as the *double aortic arch*. Two types of double aortic arches were employed. In one, the descending aorta and the ductus arteriosus were each on the left side and, in the other, the descending aorta and the ductus arteriosus were on the right side. This approach had shortcomings since it did not take into account the rare instances in which the descending aorta and the ductus arteriosus are on contralateral sides of the body.

Kirklin and Clagett (1950) essentially extended this classification to overcome these deficiencies. In the following classification, which is modified from the one proposed by them, a more primitive and hypothetical form of double aortic arch is used as a basic pattern. From this, all the known patterns of the aortic arch system may be derived. The proposed *basic pattern* (Figure VI-146a), is a double aortic arch having both a left and a right ductus arteriosus. The descending aorta is in a neutral position but, in the development of the forms derived from the basic pattern, the descending aorta deviates to one side or the other. In addition, by either atresia or disappearance of certain parts of the basic pattern, the various patterns of the aortic arch system may be derived and related to one another. With rare exceptions, the ductus arteriosus of one side disappears, and the descending aorta deviates to one side. Four basic subgroups thus result. Each subgroup has a double aortic arch with different position of the ductus and the descending aorta. When the descending aorta deviates to the right,

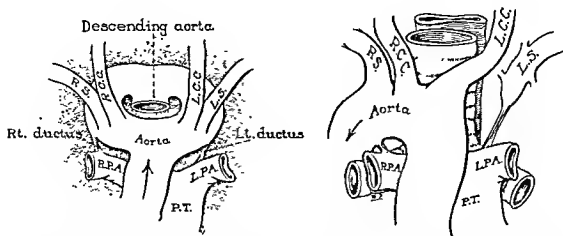


Figure VI-146. *a* Double aortic arch and double ductus arteriosus. This is a hypothetical form representing the basic pattern from which the various anatomic forms of the aortic arch system may be derived. *b* Ghon's case of double ductus arteriosus. Note a right aortic arch and right descending aorta, a right ductus which inserts into the right arch, and the left subclavian artery attached to an obliterated left-sided ductus arteriosus. (Modified from illustration of Ghon.)

it has the following characteristics. The upper portion of the descending aorta lies on the right side of the thorax, to the right of the esophagus. In the lower part of the thorax, usually at the level of the body of either the eighth or ninth thoracic vertebra, the aorta crosses to the left behind the esophagus and then emerges from the thorax through the aortic hiatus of the diaphragm.

Classification

(After Kirklin and Clagett, 1950)

Basic pattern: Double aortic arch and double ductus arteriosus.

Subgroup A: Left-sided ductus arteriosus and left-sided descending aorta.

Subgroup B: Left-sided ductus arteriosus and right-sided descending aorta.

Subgroup C: Right-sided ductus arteriosus and right-sided descending aorta.

Subgroup D: Right-sided ductus arteriosus and left-sided descending aorta.

Apparently, no case of a functioning double aortic arch with bilateral ductus (Figure VI-146a) has been described, but malformations which are closely related to it are known.

The case of Breschet, which was reproduced as Figure 30 in Poynter's monograph (1916) on aortic and arterial anomalies, showed an obliterated ductus on each side. The aortic arch pattern was otherwise normal. The case of Ghon (1908) had but one aortic arch. This and the descending aorta were both on the right side (Figure VI-146b). Poynter mentioned the cases of Hildebrand and of Holst in which the left subclavian artery arose from a patent ductus arteriosus. McKim and Wiglesworth (1954) reported 3 examples of absence of the left pulmonary artery; 2 of the patients had anatomic tetralogy of Fallot and 1, a large ventricular septal defect. In each instance the pulmonary trunk continued as the right pulmonary artery, the aortic arch was on the right side, and the first branch of the aorta was a left-sided innominate artery from which arose the left common carotid and left subclavian arteries as well as the obliterated ductus arteriosus. The lower end of the left-sided obliterated ductus arteriosus communicated with the left pulmonary artery at the hilus of the left lung. In one of the cases, a right ductus arteriosus joined the aortic arch and the right pulmonary artery. In addition to this single case of established bilateral ductus arteriosus, right-sided ductus arteriosus probably was present in one other case in McKim and Wiglesworth's group. These authors support the view that with absence of the right pulmonary artery, as in the case of Jew and Gross (1952), the ductus arteriosus is bilateral. In the case of Jew and Gross (1952), the aortic arch was interrupted

and the pulmonary trunk gave origin only to the left pulmonary artery and a left-sided ductus arteriosus. The author has observed 6 cases of bilateral ductus arteriosus. In each case both pulmonary arteries were present and only one arch or an interrupted aortic arch existed.

SUBGROUP A: LEFT-SIDED DUCTUS ARTERIOSUS AND LEFT-SIDED DESCENDING AORTA

The vast majority of patterns of the aortic arch system belong to this subgroup. They are related to the double aortic arch of the basic pattern as follows: The right ductus disappears and the descending aorta deviates to the left. The functioning double aortic arch illustrated in Figure VI-147a represents a basic pattern from which all members of subgroup A may be derived.

1. **Functioning Double Aortic Arch** (Figures VI-147a and b). The double aortic arch has the following characteristics: The ascending aorta arises normally from the left ventricle and then divides into two arches, a left and a right. The left or so-called anterior arch closely follows the course of the normal aortic arch. It passes in front of the trachea and over the left major bronchus to join the descending aorta which lies on the left side of the body. The right or so-called posterior arch passes over the right major bronchus and then turns rather abruptly to the left, dorsal to the esophagus and ventral to the vertebral column. It joins the left arch either to the left of, or dorsal to, the esophagus at the point at which the latter arch joins the descending aorta. The branches of the aortic arches are symmetrically arranged. The right common carotid and the subclavian arteries arise independently, in that order, ventrodorsally from the right aortic arch. Similarly, the left common carotid and subclavian arteries arise from the left arch. The ductus arteriosus is inserted into the left arch between the origin of the left subclavian artery ventrally and the junction of the left and right arches dorsally. The inferior attachment of the ductus arteriosus is to the left pulmonary artery.

When a functioning double aortic arch exists, the two arches are often of unequal diameter, the right one usually being wider (Figure VI-147b; Curnow, 1875; Blincoe *et al.*, 1936; Wolman, 1939; Herbut, 1943, Case II; Neuhauser, 1946; Gordon, 1947, Case 3; Sweet *et al.*, 1947, Case 1; Sakla, 1950). Occasionally the two arches are of approximately equal caliber (Schall and John-

son, 1940, Crystal *et al.*, 1947), or the left arch is larger (Gordon, 1947, Case 4). While double aortic arch may be found in the other subgroups, it occurs most commonly in subgroup A (Griswold and Young, 1949). Such a malformation may be visualized by angiography (Skop, 1949).

2. **Focal Atresia of One Aortic Arch.** An accentuation of the inequality of the two aortic arches leads to anomalies in which part of one of the arches is atretic and resembles a fibrous cord. As a rule, the atresia is situated in the left arch but it is theoretically possible for portions of the right arch, instead, to be atretic. Three anatomic forms are recognized, depending upon the site of the atretic segment of the left arch. Hypothetically, the atresia may involve that part of the left aortic arch which lies between the origins of the left common carotid artery and the left subclavian artery (Figure VI-147c), it usually lies between the origin of the left subclavian artery and the aortic insertion of the ductus arteriosus (Figure VI-147d; Thomson, quoted by Turner, 1862; Brigham, 1922, Ewald, 1926, Arkin, 1936, Griswold and Young, 1949, Case 1), or it may involve the most distal part of the left arch between the aortic insertion of the ductus arteriosus and the region of the posterior junc-

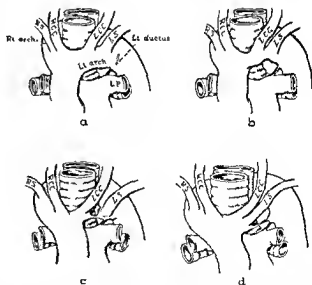


Figure VI-147. Vascular rings, subgroup A. (Left ductus, left descending aorta.) (From Edwards, 1948b. Reproduced by permission of the W. B. Saunders Company.) a, Functioning double aortic arch in which the two arches are of about equal size. b, Functioning double aortic arch in which the left arch is smaller than the right. c, A double aortic arch with atresia of the left arch between the left common carotid and left subclavian arteries. (Hypothetical form.) d, Double aortic arch with atresia of the left arch between the ductus arteriosus and the origin of the left subclavian artery.

tion of the left and right aortic arches (Watson, 1877).

3. **Right-Sided Aortic Arch with Retro-esophageal Segment and Left-Sided Descending Aorta.** In cases of double aortic arch in which a portion of one arch is atretic but recognizable, it is evident that the atresia occurred rather late during fetal life or after birth. Should obliteration of a portion of a double aortic arch take place relatively early in fetal life, the atretic segment may no longer be present as an identifiable structure at the time of birth. The double arch then does not exist as a continuous structure. Such variants of the double aortic arch are included in the following forms.

a. **Right-sided aortic arch with retro-esophageal segment and left-sided descending aorta; left subclavian artery originating from aortic diverticulum.** The segment of the left aortic arch between the origin of the left common carotid artery and the left subclavian artery disappears, giving the pattern shown in Figure VI-148a. There is but one complete aortic arch, the right, which passes over the right bronchus and then turns to the left at about the level of the body of the third or fourth thoracic vertebra, between the esophagus ventrally and the spinal column dorsally. Either directly dorsal to the esophagus or to its left, the aortic arch joins the descending aorta which usually lies to the left of the midline. The first three branches of the aortic arch are the left common carotid, the right common carotid, and the right subclavian arteries, in that order ventrodorsally. The left subclavian artery arises as the fourth branch of the aorta from a saecular outpouching that lies at the left superior angle of the junction of the right aortic arch with the descending aorta. The diverticulum usually lies against the left side of the esophagus, and into its lower anterior aspect is inserted the superior portion of the ductus arteriosus. The inferior attachment of the ductus arteriosus is to the left pulmonary artery (Quain, 1844; Turner, 1862; Herringham, 1891; Abbott, 1892; Reid, 1914; Ewald, 1926, Case 4; Pense, 1930; Bedford and Parkinson, 1936; Herbut, 1943, Case 10).

This condition is comparable with that illustrated in Figure VI-147c in which there was predicted atresia of the segment of the left aortic arch between the origins of the left common carotid and left subclavian arteries, and in which the atretic segment would be identifiable as a fibroid cord. Because the atretic segment is no longer identifiable, on casual examination one might not identify the anomaly as a variant of the double

aortic arch. The aortic diverticulum that gives rise to the left subclavian artery and serves as a point of attachment for the ductus arteriosus should be regarded as a patent posterior portion of a left aortic arch. The segment of the left aortic arch between the origin of the left subclavian and common carotid arteries disappeared during early embryonic life and is not identifiable.

Despite the absence of the symmetrically constricting effects of a continuous double aortic arch, a vascular ring is present about the trachea. The ring is formed by the right aortic arch on the right, the retro-esophageal segment of the right aortic arch dorsally, the aortic diverticulum and the ductus arteriosus on the left, and the bifurcation of the pulmonary trunk ventrally. The subclavian artery plays no role in formation of the vascular ring. In such instances, a break in the continuity of the vascular ring may be accomplished by the division of the ductus arteriosus, which allows left lateral expansion of the trachea and the esophagus. The procedure also allows the bifurcation of the pulmonary trunk to lead away from the ventral surface of the trachea, with relief of pressure against that tube. The left common carotid artery arises to the right of the midline and crosses ventral to the trachea to reach its usual position on the left side of the superior mediastinum. Gross and Ware (1916) and Gross (1946, 1947) recommended dislocating this artery if it compresses the trachea unduly.

b. **Right-sided aortic arch with retro-esophageal segment and left-sided descending aorta; left subclavian artery originating from left innominate artery.** Referring to the double arch of this subtype (Figure VI-147a), it is evident that if the portion of the left aortic arch between the origin of the left subclavian artery and the insertion of the ductus arteriosus disappears, the pattern appears as in Figure VI-148b. There is one aortic arch, the right. This passes over the right major bronchus, then turns to the left and passes between the esophagus and the spinal column, as in the anomalies previously described. Dorsally, or to the left of the esophagus, it joins the left-sided descending aorta. At the junction of the aortic arch and descending aorta, there is a diverticulum into which the ductus arteriosus inserts (Gruber, 1912, Case 2). The left subclavian artery does not arise from the diverticulum but instead arises from a left-sided innominate artery in common with the left common carotid artery. The left innominate artery is the first branch of the aortic arch, the second and third branches

being the right common carotid and right subclavian arteries, respectively.

4. **Left-Sided Aortic Arch and Left-Sided Descending Aorta.** The types of anomalies that have been discussed under Subgroup A thus far were characterized, not only by the presence of the ductus arteriosus on the left side, but also by the presence of a right-sided aortic arch either alone or associated with a left-sided aortic arch. Since the cephalic part of the descending aorta lay either in the midline or to the left of the midline, the dorsal portion of the right aortic arch had a horizontal segment, posterior to the esophagus, which was directed toward the descending aorta. In the remaining types of vascular patterns to be considered in Subgroup A, the left aortic arch is the only one that is present as a continuous functioning vessel. Portions of the right arch have disappeared.

a. **Left-sided aortic arch and left-sided descending aorta; right subclavian artery arising from distal portion of aortic arch or from the descending aorta.** This pattern is characterized by the disappearance of the segment of the right portion of the double aortic arch between the origins of the right common carotid and the right subclavian arteries. Consequently, the first branch of an otherwise normal left-sided aortic arch is the right common carotid artery rather than the innominate artery. The second and third branches of the arch are the left common carotid and the left subclavian arteries, respectively. The right subclavian artery arises as the fourth branch of the aorta from either the aortic arch or the cephalic part of the descending aorta (Figure VI-148c). The origin of this artery is frequently wider than the rest of the intrathoracic portion of the vessel, a feature that is not unexpected since the origin of the right subclavian artery in this anomaly represents the most dorsal portion of a right-sided aortic arch. From its origin on the left side of the midline, the right subclavian artery proceeds cephalically and to the right in an oblique direction. It crosses the midline, usually by passing between the esophagus ventrally and the spinal column dorsally (Thomson, 1893; Holzapfel, 1899; Poynter, 1916; Goldbloom, 1922; Dolgopel, 1934). Less often, as in Bayford's case (1794), the artery lies between the esophagus and the trachea as it passes from the left side of the body to the right side, and even less commonly does it cross ventral to the trachea.

Origin of the right subclavian artery as the fourth branch from an otherwise normal aorta is

the most frequent of the anomalies under consideration. It may occur as often as once in every 200 persons. Usually it does not give rise to symptoms. When present, symptoms are related to interference with the function of the esophagus. While usually no other malformations are associated with this anomaly, Breaun and Neuhauser (1947) described this malformation in 3 infants in association with patent ductus arteriosi. In only one of these did the right subclavian artery seem to cause dysphagia. If the function of the esophagus is compromised by the anomalous artery, the latter should be divided.

This anomaly may be associated with coarctation of the aorta either distal or proximal to the origin of the anomalous artery (Sealy, 1951; Kroeker *et al.*, 1954, see Section on Coarctation, page 450). Rupture of an aneurysm of an anomalous right subclavian artery was reported by Richards and Elliott (1957).

b. **Left-sided aortic arch and left-sided descending aorta, normal arch and branches.** It seems logical to consider the features of the normal aorta at this point since it too can be regarded as a modification of the double aortic arch. If one assumes that the double aortic arch of Subgroup A is modified so as to result in loss of the right arch between the origin of the right subclavian

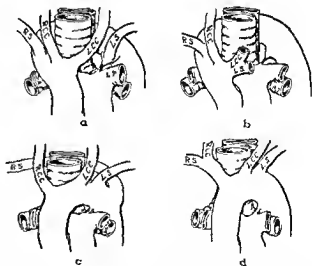


Figure VI-148. Vascular rings, subgroup A, continued. (From Edwards, 1948b. Reproduced by permission of the W. B. Saunders Company.) a. A right aortic arch with retro-esophageal segment. Left descending aorta. Left ductus inserts into aortic diverticulum from which left subclavian artery arises. b. Right aortic arch with retro-esophageal segment. Left descending aorta. Left ductus inserts into aortic diverticulum. Left subclavian artery originates from left innominate artery. c. Right subclavian artery arises as a fourth branch of an otherwise normal aorta. d. Normal aorta.

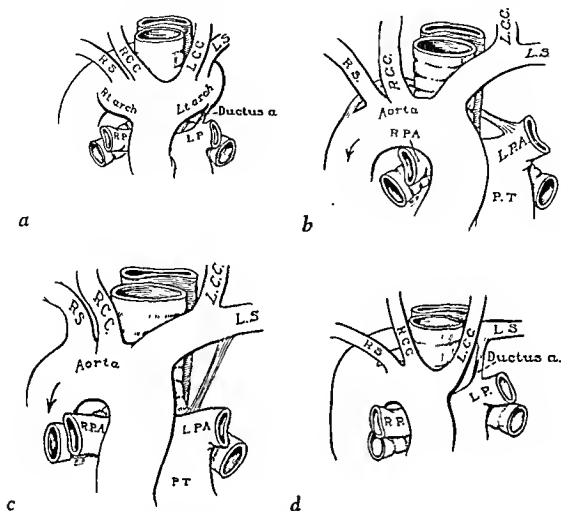


Figure VI-149. Vascular rings, subgroup B. (Left ductus, right descending aorta.) *a*. Functioning double aortic arch. (From Kirklin and Clagett, 1950.) *b*. Right aortic arch. Right descending aorta. Left ductus passing behind esophagus to aorta. *c*. Right aortic arch. Right descending aorta. Left ductus arteriosus inserts into left subclavian artery which originates from left innominate artery. *d*. Right arch. Right descending aorta. Left ductus arteriosus inserts into left subclavian artery which arises as the fourth branch of the aorta. (From Kirklin and Clagett, 1950.)

artery and the descending aorta, one arrives at the structure of the normal aorta (Figure VI-148d). The first branch of the aortic arch is the innominate artery which soon divides into the right common carotid and right subclavian arteries. The second branch is the left common carotid artery and the third is the left subclavian artery. The descending aorta lies on the left side and no undue compression upon the trachea or the esophagus is caused by the aortic arch or its branches. The ductus arteriosus extends from the left pulmonary artery to the aorta at a point beyond the origin of the left subclavian artery.

c. *Left-sided aortic arch and descending aorta; left pulmonary artery arising from right pulmonary artery.* This rare type of vascular ring was

described by Potts and associates (1954) and by Welsh and Munro (1954). A similar case was submitted to the author by Dr. J. J. Likos. The aorta is normal. The pulmonary trunk continues only as the right pulmonary artery. The ductus arteriosus, which is on the left side, arises from the left upper aspect of the pulmonary trunk. The left pulmonary artery arises to the right of the midline from the right pulmonary artery. The left pulmonary artery crosses over the superior aspect of the right main bronchus and, after passing behind the trachea and in front of the esophagus (described in Welsh and Munro's case as passing behind the esophagus), enters the left lung. The left pulmonary artery compresses the right main bronchus and the trachea as it passes

these structures. The probable developmental basis for this type of malformation is failure of development of the left pulmonary branch from the left sixth aortic arch. The intact left ductus arteriosus indicates that the left sixth arch itself had been developed. The left pulmonary artery probably takes origin from the common plexus of vessels which initially supplied the lung buds at a stage before the two lungs are distinct from each other.

SUBGROUP B: LEFT-SIDED DUCTUS ARTERIOSUS AND RIGHT-SIDED DESCENDING AORTA

In a relatively small number of cases, the aortic arch pattern consists of the ductus arteriosus on the left side and the descending aorta on the right side. The basic pattern of this subgroup is the functioning double aortic arch, as illustrated in Figure VI-149a.

1. Functioning Double Aortic Arch (Shaw, 1897, Herrmann, 1928, Herbut and Smith, 1943, Kaiser, 1948, Griswold and Young, 1949, Case 2). As in the other forms of double aortic arch, an aortic arch passes over each bronchus. The left arch is the one which is retro-esophageal, joining the right arch on the right side of the midline to form the descending aorta. The latter structure is on the right. Each arch gives rise to its respective common carotid and subclavian arteries, in that order. The ductus arteriosus is on the left side, running from the left pulmonary artery to the left arch, it inserts into the latter at a point just beyond the origin of the left subclavian artery (Figure VI-149a).

2. Partial Atresia of One Arch. The case of Issajew (1931) is an example of double aortic arch of Subgroup B with atresia of one arch. The left arch was atretic between the origins of the left subclavian artery and the left common carotid artery.

3. Right Aortic Arch, Right Descending Aorta and Left-Sided Ductus Arteriosus. This pattern of the aortic arch is the most common of those characterized by a left-sided ductus arteriosus and a right-sided descending aorta. The aortic arch and the descending aorta are both on the right side. The ductus arteriosus arises from the left pulmonary artery and may insert either into the aorta or into the left subclavian artery. Three patterns are identifiable, depending upon the location of interruption of the left portion of the double arch illustrated in Figure VI-149a.

a. Right arch; right descending aorta; left duc-

tus inserting into the aorta. The left arch of the double aortic arch of Subgroup B is interrupted between the origin of the left subclavian artery and the insertion of the ductus arteriosus (Figure VI-149b). The arch is on the right. Its first branch is a left innominate artery from which the left common carotid and left subclavian arteries arise. The ductus passes dorsal to the esophagus to the right side to insert into the aorta at the junction of the arch with the descending aorta (Ewald, 1926, Case 2, Halpert *et al.*, 1949). This form may be associated with symptoms of tracheal and esophageal compression, as emphasized by Neuhauser (1949).

b. Right arch; right descending aorta; left ductus inserting into left subclavian artery originating from left innominate artery. In the form just described, the left arch of the double arch of Subgroup B was interrupted between the left subclavian artery and the ductus arteriosus. The left arch is interrupted dorsal to the insertion of the ductus into it (Figure VI-149c). The pattern is like that in Figure VI-149b except that the ductus inserts into either the left innominate or the left subclavian artery. This pattern may be seen in the tetralogy of Fallot when a right aortic arch exists (Bahnsen and Blalock, 1950).

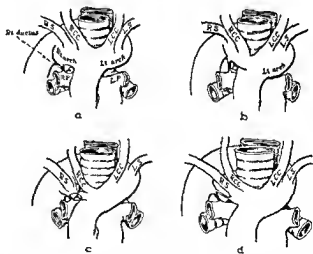


Figure VI-150. Vascular rings, subgroup C. (Right ductus, right descending aorta) (From Edwards, 1948b. Reproduced by permission of the W. B. Saunders Company.) a. Functioning double aortic arch in which both arches are of about equal size. (Hypothetical form.) b. Functioning double aortic arch in which the right is the narrower of the two arches. (Hypothetical form.) c. Double aortic arch with atresia of the right arch between the right common carotid and right subclavian arteries. (Hypothetical form.) d. Double aortic arch with atresia of right arch between the right subclavian artery and insertion of right ductus arteriosus. (Hypothetical form.)

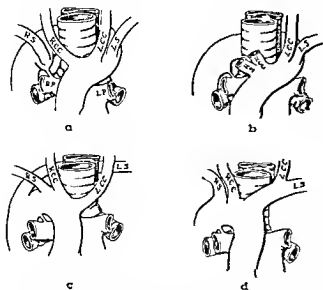


Figure VI-151. Vascular rings, subgroup C, continued. (From Edwards, 1948b. Reproduced by permission of the W. B. Saunders Company.) *a* Left aortic arch with retro-esophageal segment. Right descending aorta. Right ductus arteriosus inserts into aortic diverticulum from which right subclavian artery arises. *b* Left aortic arch with retro-esophageal segment. Right descending aorta. Ductus inserts into aortic diverticulum. Right subclavian artery originates from right innominate artery. *c* Right aortic arch. Right descending aorta. Left subclavian artery originates as fourth branch of aorta. *d* Right aortic arch. Right descending aorta. Left innominate artery.

c. Right arch; right descending aorta, left ductus inserting into left subclavian artery originating as fourth branch of the aorta (Figure VI-149d). If the left arch of the double arch of Subgroup B is interrupted between the origins of the left common carotid and left subclavian arteries, the left subclavian artery arises as the fourth branch of the aorta or from a diverticulum of the cephalic part of the descending aorta on the right side of the body and then crosses to the left, dorsal to the esophagus. The ductus arteriosus inserts into the base of the left subclavian artery or into the diverticulum from which it arises (Gruber, 1912, Case 1; Biedermann, 1931).

In the case described by Humphreys (1948), a patent ductus arteriosus inserted into the left subclavian artery which arose as the fourth branch of the aorta. The patient of Siekert (1949) a woman aged 23 years with the Eisenmenger complex, had a right arch which gave rise to the left common carotid, the right common carotid and the right subclavian arteries, proceeding ventrodorsally in the order mentioned. The aorta thus proceeded to the midline where it was joined by a vessel which was continuous with a left-sided

patent ductus and from which the left subclavian artery arose. Though Siekert claimed that the ductus inserted into the aorta, we believe that the posterior portion of the left arch was retained and the ductus inserted into it and that the left subclavian artery arose from the remnant of the left arch.

d. Right arch; right descending aorta; left ductus inserting into isolated left subclavian artery. In a case observed by the author, a patient with the anatomic tetralogy of Fallot had a right aortic arch in which the branches ventrodorsally were the left common carotid, right common carotid, and right subclavian arteries. The descending aorta was on the right. The left subclavian artery did not connect with any portion of the aorta, but instead arose from a narrowly patent left-sided ductus arteriosus. Except for the absence of a ductus arteriosus on the right, this case presents essentially the mirrored image of the case of Ghon in which the ductus arteriosus was bilateral.

4. Left Arch, Left Ductus and Right Descending Aorta. In malformations of Subgroup B with but one arch, so far considered, the right arch was present since part or all of the left arch had become obliterated. If parts of the right arch were to disappear while the left arch remained intact, the malformations would be represented by a left arch, a left ductus arteriosus and a right descending aorta. Though such malformations are hypothetical possibilities, it seems unlikely that they would occur.

SUBGROUP C: RIGHT-SIDED DUCTUS ARTERIOSUS AND RIGHT-SIDED DESCENDING AORTA

I. Functioning Double Aortic Arch. The basic pattern of Subgroup C is the functioning double aortic arch. Though there is no established example of this form of malformation, the second case of Sweet and associates (1947) is suggestive of it. No ductus arteriosus was found on either side during operation on this patient. Had a right-sided ductus arteriosus been discovered, the criteria for the functioning double aortic arch of Subgroup C would have been fulfilled. Though the existence of this form is still hypothetical, derivatives of it are known and its anatomic characteristics may be defined (Figure VI-150a).

The ascending aorta bifurcates ventral to the trachea. The left and right arches pass over the respective major bronchi. Since the cephalic part of the descending aorta lies on the right, the left arch crosses to the right, dorsal to the esophagus, to join with the right arch as the latter blends

with the descending aorta. The subclavian and common carotid arteries arise independently from the respective arches. The ductus runs between the right pulmonary artery and the right arch and is inserted into the latter just distal to the origin of the right subclavian artery. In the hypothetical form illustrated in Figure VI-150a, the two arches are portrayed as being of equal caliber. Figure VI-150b illustrates a functioning double aortic arch in which the left is the larger of the two. This pattern of the arches resembles that in the case of Sweet and associates.

2. **Partial Atresia of an Arch.** In Subgroup C, patterns characterized by partial atresia of one of the two arches have not been described and their existence is hypothetical. In Figure VI-150c the atresia is shown between the origins of the right common carotid and subclavian arteries, while in Figure VI-150d, the atresia lies between the right subclavian artery and the right-sided ductus arteriosus. Malformations are known in which the right arch has "dropped out" at locations corresponding to the levels of atresia represented in these two figures. These forms follow.

3. **Left-Sided Aortic Arch with Retro-esophageal Segment and Descending Aorta on Right.**
a. Right subclavian artery originating from aortic diverticulum. If the segment of the right arch represented as atretic in Figure VI-150c is lost, the following pattern is encountered (Figure VI-151a). There is but one continuous arch, the left. After crossing the left major bronchus, this arch deviates to the right to pass dorsal to the esophagus and to join the descending aorta on the right side. At the junction of the left arch with the descending aorta, a diverticulum represents a remnant of the posterior extremity of the right arch. Into this structure the ductus arteriosus is inserted, and the right subclavian artery arises from the diverticulum. This form of anomalous aorta has been reported (Edwards, 1948a).

b. Right subclavian artery originating from a right-sided innominate artery (Figure VI-151b). If the right arch is interrupted between the origins of the right subclavian and right carotid arteries, the right subclavian artery arises from the aortic diverticulum. If, on the other hand, the right arch disappears posterior to the origin of the subclavian artery, that vessel arises in common with the right common carotid artery from a right-sided innominate artery. The arch is on the left side and, after passing over the left bronchus, passes dorsal to the esophagus to join the descending aorta on the right side.

4. **Right-Sided Aortic Arch and Descending**

Aorta on Right Side. If in the basic form of this subgroup (Figure VI-150a), the right arch remains intact but parts of the left arch disappear, the following forms are achieved.

a. Left subclavian artery originating as fourth branch of the right aortic arch (Figure VI-151c). (See Lockwood, 1884, Kopsch, 1914, Dittich, quoted by Renander, 1926.) If the left arch is interrupted between the origins of the left common carotid and left subclavian arteries, the left subclavian artery loses its connection with the ventral part of the aorta and arises as the fourth branch of the aorta. It then crosses dorsal to the esophagus from right to left. The right-sided ductus inserts into the aortic arch between the origins of the right and left subclavian arteries.

b. Left subclavian artery originating from left-sided innominate artery (Figure VI-151d). (See Epstein, 1886; Reid, 1914, Case 2; Assmann, 1924, Ewald, 1926, Case 1; Sprong and Cutler, 1930.) If the left arch should disappear dorsal to the origin of the left subclavian artery, the mirrored image of the normal would be achieved. The pattern consists of a right arch with a right descending aorta, a ductus arteriosus on the right side, and a left innominate artery. Though this pattern of aortic arch may occur in the absence of a cardiac malformation, it is usually associated with the tetralogy of Fallot. As Bahnson and Blalock have emphasized, when a right arch and right descending aorta are found, the ductus arteriosus need not be on the right side but may be on the left as in Subgroup B. Nevertheless, some of the cases have a right ductus.

SUBGROUP D: RIGHT-SIDED DUCTUS ARTERIOSUS AND LEFT-SIDED DESCENDING AORTA

This group may be regarded as the mirrored

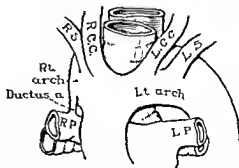


Figure VI-152. Vascular rings, subgroup D. (Right ductus, left descending aorta.) The functioning double aortic arch which is illustrated is a hypothetical form from which other forms may be derived. All derivatives are as yet hypothetical. (From Kirklin and Clagett, 1950.)

image of Subgroup R. The basic pattern of Subgroup D is likewise a functioning double aortic arch (Figure VI-152). The right arch crosses the midline dorsal to the esophagus. It then joins with the left arch to form the descending aorta which lies on the left. The

ductus arteriosus is a right-sided structure, inserting into the right arch posterior to the take-off of the right subclavian artery. Apparently, no example of Subgroup D has been reported, but the double arch and derivatives of it remain as hypothetical possibilities.

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Congenital Malformations

I. Malformations of the Thoracic Veins

JESSE E. EDWARDS

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SYSTEMIC VEINS

Persistent Left Superior Vena Cava

WITH RARE EXCEPTIONS, malformations of the systemic intrathoracic veins cause no functional disturbance. The most common of these malformations is persistent left superior vena cava. In this condition the right innominate vein is formed in a normal manner by the union of the right internal jugular and subclavian veins. It does not receive the left innominate vein to form the superior vena cava. Instead, it descends in the position of the superior vena cava and, after receiving the azygos vein, enters the right atrium as the superior vena cava does normally. On the left side, the left innominate vein is formed by its usual tributaries. Instead of crossing to the right, the left innominate vein descends vertically to enter the thorax. In this position it is called left superior vena cava. Here it passes ventrally to the aortic arch and the root of the left lung. At the inferior level of the root of the left lung, the left superior vena cava turns to the right, pierces the pericardium and reaches the left aspect of the left atrioventricular groove. Here it becomes continuous with the coronary

sinus (Figure VI-153a). The latter, by virtue of carrying the additional blood coming to it by the anomalous connection, is wider than normal. The coronary sinus terminates in the right atrium. Therefore, though the course of blood from the left arm and left side of the head and neck is abnormal, the blood finally reaches the right atrium (Chaffey, 1885).

Usually the *hemiazygos vein* joins the left superior vena cava after arching over the left main bronchus to form a mirrored image of the normal arrangement of the azygos vein and superior vena cava on the right. Rarely the *hemiazygos vein* joins the uppermost part of an incomplete left superior vena cava, while the lowermost end of the left superior vena cava joins the coronary sinus. A persistent left superior vena cava may be an isolated malformation or it may be associated with any of the known malformations of great arteries.

The papers of Halpert and Coman (1930), Atwell and Zoltowski (1938) and Winter (1954) contain extensive bibliographies on malformations of the superior vena cava. The cases of Hepburn (1887) and Papez (1938) had the usual pattern of a persistent left superior vena cava as well as a vessel which connected the two in-

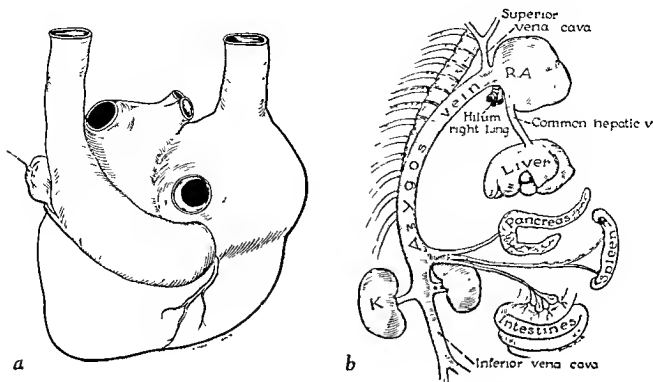


Figure VI-153. *a.* Persistent left superior vena cava. Posterior view of heart showing continuity of persistent left superior vena cava with dilated coronary sinus. *b.* Union of inferior vena cava with azygos vein. Absence of portal vein. The splanchnic veins drain into the abdominal systemic vein. A common hepatic vein runs from the liver to the right atrium. (From a case reported by Hickman and associates, 1949, occurring in a dog. Reproduced by permission of the Wistar Institute, publishers of *Anatomical Record*.)

nominate veins in the lower cervical region. In the cases reported by Greenfield (1876), Halpert and Coman (1930) and Atwell and Zoltowski (1938) the *right superior vena cava* was absent and the venous system in the neck was essentially a mirrored image of the normal. The right innominate vein crossed to the left and joined the left innominate vein to form a left superior vena cava. The latter then followed the usual course of a left superior vena cava and terminated in the coronary sinus.

The superior vena caval system may have anomalous connections with other structures. In Nabarro's (1903) Case 2, a *left hepatic vein* joined the left side of the coronary sinus near the termination of a persistent left superior vena cava. The termination of a pulmonary vein in the coronary sinus or in the caval system is discussed in the section dealing with Anomalous Drainage of the Pulmonary Veins.

The association of a persistent left superior vena cava with atresia of the right atrial ostium of the coronary sinus is discussed under Malformations of the Coronary Vessels.

Connection of a Vena Cava with Left Atrium

In cases of *cor biloculare*, bilateral superior venae cavae are common and the left vein frequently joins the left side of the common atrium. Under rare circumstances, a persistent superior vena cava may join the left atrium if two atria are present (MacKenzie, 1880, Hu, 1929, Potter, 1948, Case 3, Hurwitt *et al.*, 1955; Tuchman *et al.*, 1956). In this way venous blood is carried directly to the left side of the heart. The patient of Haeger and associates (1955) had this anomaly as well as a ventricular septal defect. Whenever the left superior vena cava joins the left atrium or the left side of a common atrium, the coronary sinus is absent. The reason is that the coronary sinus, when present, represents the terminal portion of the left superior vena cava. Rarely the inferior vena cava joins the left atrium as an isolated malformation (Gardner and Cole, 1955).

Continuity of Azygos Vein and Inferior Vena Cava

The inferior vena cava is subject to many variations (E. A. Edwards, 1951). Of interest, with regard to the thoracic veins, is the rare instance in which the inferior vena cava, after receiving the renal veins, fails to follow its usual course. Instead, it becomes continuous with the lower portion of the azygos vein (Griffith, 1891; Miller, 1925; Anderson *et al.*, 1955). Because the azygos vein carries the additional blood brought to it by the inferior vena cava, it becomes greatly dilated. No functional disturbance results since the venous blood from the lower part of the body is carried to the right atrium. Emerging from the liver in the usual location of the terminal portion of the inferior vena cava is a narrow

vein representing a common hepatic vein.

The author observed a patient with situs inversus, atrial septal defect and anomalous connection of the left-sided pulmonary veins who also had anomalies of the systemic veins. Bilateral superior venae cavae were present. The one on the right side received the inferior vena caval blood by way of a large right-sided hemiazygos vein. The blood from the right sided superior vena cava then was delivered through the coronary sinus into the left-sided (venous) atrium. In a dog with these venous abnormalities, Hickman and associates (1949, Figure VI-153b) also noted *absence of the portal vein*. They referred to two human cases with absence of the portal vein (Abernethy, 1793; Kieman, 1833). Putschar (1938) described a case in which the umbilical vein bypassed the portal system and entered the right atrium.

PULMONARY VEINS

Developmental Background

Anomalies of the pulmonary veins may best be understood from a review of their development (Edwards and Helmholz, 1956).

Inasmuch as the lungs are derived as a specialized part of the alimentary canal, these organs initially possess capillary-venous systems in common with the alimentary canal (Brown, 1913; Butler, 1952a). The capillary plexus, the so-called splanchnic plexus, connects with veins of both somatic and visceral types. The somatic veins are represented by the cardinal system from which such structures as the superior vena cava, the innominate veins and the coronary sinus are derived. The visceral system of veins are represented by the so-called umbilico-vitelline system from which the portal and gastric veins and the ductus venosus are derived. It is thus apparent that initially there is no direct channel between the capillary plexus of the lungs and the heart, the venous drainage being through the venous systems named.

Secondarily a protrusion, from the part of the sinoatrial region of the heart that is to become the left atrium, grows toward the developing lungs (Auer, 1948). This protrusion may be termed the "common pulmonary vein" (Figure VI-154a, b and c). It makes connections with

the splanchnic plexus of capillaries of the developing lungs. As these connections become established, the original connections of the pulmonary part of the splanchnic plexus with the cardinal and umbilico-vitelline systems of veins are lost as major channels. Minor remnants of these channels persist as normal (but narrow) connections between pulmonary veins on one hand, and bronchial and portal veins on the other (Liebow, 1953).

The common pulmonary vein ultimately is incorporated by a process of differential growth into the left atrium (Figure VI-154a and c). This yields the definitive state in which the left atrium receives the four major pulmonary veins. By this incorporation the common pulmonary vein normally becomes lost as an identifiable structure.

Anomalies of the pulmonary veins may result from persistence of connection of the pulmonary portion of the splanchnic plexus with its original venous connections (Edwards, 1953; Neill, 1956). This may result either from failure of the common pulmonary vein to develop or from secondary obliteration or narrowing of it. Other anomalies result from failure of the common pulmonary vein to be normally incorporated into the left atrium. In still other instances congenitally stenosing lesions of the pulmonary veins are present. Possibly, depending on whether or not a primitive venous connection still exists, some of

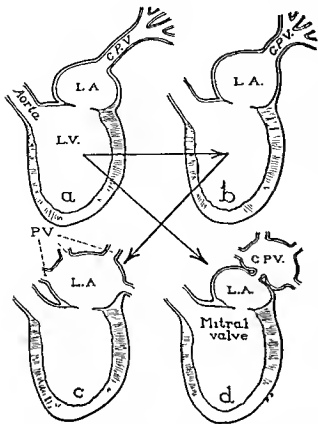


Figure VI-154. *a*, *b* and *c* demonstrate diagrammatically the normal incorporation of the common pulmonary vein and, later, of its tributaries into the dorsal wall of the left atrium (*L.A.*). If the junction of the common pulmonary vein (*C.P.V.*) and the left atrium remains essentially as represented in *a*, an accessory chamber is formed which represents the common pulmonary vein (*d*). The accessory chamber represents a dilated common pulmonary vein and the heart has the characteristics of *cor triatriatum*.

the latter lesions will or will not be associated with anomalous pulmonary venous connection.

Terminology

The term "anomalous pulmonary venous drainage" has in the past been used both anatomically and physiologically to signify a condition in which a major pulmonary venous pathway fails to join the left atrium. The abnormal pulmonary venous pathway leads either to the right atrium directly or into a tributary vein thereof.

Recent observations have indicated that anomalous pulmonary venous drainage may occur in a physiologic sense in patients who have normal connection of the pulmonary veins with the heart but in whom an atrial

septal defect exists (Swan *et al.*, 1953). Moreover, it is possible hypothetically for anatomic anomalous pulmonary venous connection to occur without functional anomalous venous drainage of the lungs. It seems appropriate to distinguish these anatomic and physiologic conditions. Therefore, as used here (Edwards *et al.*, 1953) *anomalous pulmonary venous drainage* will be regarded as a physiologic term indicating the flow of pulmonary venous blood, by whatever route, into the right atrium. The anatomic condition in which a pulmonary vein fails to join the left atrium but joins the right atrium or a systemic vein will be referred to as "anomalous pulmonary venous connection." In order to avoid confusion, it is to be emphasized that the word "connection" does not refer to the condition of the pulmonary veins at their origin in the lungs but rather to the termination of these veins.

Classification

I. Stenosis of pulmonary veins

A. Common pulmonary vein (*cor triatriatum*)

1. With normal connection
2. With anomalous connection
 - a. To right atrium
 - b. To systemic veins

B Individual veins

1. With normal connection
2. With anomalous connection

II. Anomalous pulmonary venous connection

- A. Total. Connection between left atrium and systemic veins
- B. Partial

III. Pulmonary arteriovenous fistula

- A. Intrapulmonary
- B. Connection of pulmonary artery with left atrium

Stenosis of Common Pulmonary Vein (*Cor Triatriatum*)

In this rare condition the pulmonary veins enter an accessory chamber which lies attached to the dorsal aspect of the left atrium.

Loeffler (1949) divided the cases into three groups. In one there is no communication be-

tween the accessory chamber and the left atrium. A connection exists between the accessory chamber and the right atrium or partial anomalous connection to some of the systemic veins. In the classification just presented, such cases are classified as total anomalous connection of pulmonary veins although, developmentally, they are related to true cor triatriatum (Edwards *et al.*, 1951).

In Loeffler's second group, one or several small openings, each only a few millimeters wide, exist between the floor of the accessory chamber and the roof of the left atrium. Death in infancy or childhood is common in such cases (Edwards *et al.*, 1951, Barnes and Finlay, 1952, Doxiadis and Emery, 1953). Hartmann's (1955) patient lived to the age of 12 years and Borst's (1905) patient, to 38 years.

Loeffler's third group (Griffith, 1903; Loeffler, 1949) is characterized by a relatively wide connection between the accessory chamber and the left atrium. The patients usually live to adult life.

The two chambers, the one which receives the pulmonary veins and the one caudal to it, taken together present the appearance of a left atrium and an accessory left atrium

(Figures VI-154d and VI-155). The chamber that lies caudal connects with the auricular appendage and, by way of a normal mitral valve, with the left ventricle. The appearance of two left atria is responsible for application of the name "cor triatriatum" to this condition.

The cause of the malformation is controversial (Parsons, 1950). One view holds that it results from faulty development of the atrial septum, that the accessory chamber is a space between interatrial septa I and II (Patten and Taggart, 1929). The other view, shared by the author, is that the "accessory" atrium is to be regarded as a common pulmonary vein which has failed to become incorporated into the dorsal wall of the left atrium as it does in the normal embryo (Figure VI-154). The narrow opening between the left atrium and the accessory atrium probably represents the original point of junction between the left atrium and the common pulmonary vein of the embryo.

Functionally, stenosis of the common pulmonary vein is similar to mitral stenosis in that it represents a barrier to pulmonary ve-

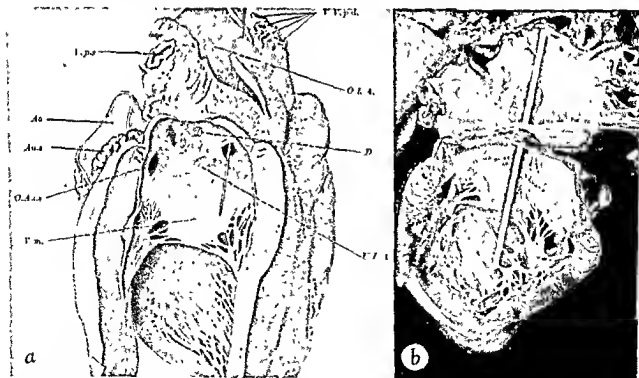


Figure VI-155. Cor triatriatum. *a*, Congenital stenosis of the common pulmonary vein (the case of Borst). An accessory chamber representing a dilated common pulmonary vein receives the four pulmonary veins and communicates by way of a narrow opening with the left atrial chamber. *b*, Stenosis of the common pulmonary vein in a female infant aged 7½ months. This specimen is virtually identical with that of Borst, illustrated in *a*.



Figure VI-156. Cor triatriatum with communication of accessory chamber with right atrium. Left side of heart. Above the left atrium lies the "accessory left atrial chamber" which receives the pulmonary veins. The left lower probe is in the narrow opening to the true left atrium. The right upper probe disappears in the opening between the accessory left atrial chamber and the right atrium.

nous drainage. A feature dissimilar from mitral stenosis is that the mitral valve is normally formed and so mitral insufficiency is not present. On hypothetical grounds, the patient with congenital stenosis of the common pulmonary vein should exhibit the same clinical features as the patient with mitral stenosis, including a presystolic murmur but with the exception that a systolic murmur of associated mitral insufficiency should not be present in congenital pulmonary venous stenosis. This was the case in Borst's patient.

The suggestion that *surgical relief* of the obstruction could be accomplished by enlargement of the opening between the left atrium and the accessory chamber was made by Barnes and Finlay (1952) and by Pedersen and Therkelsen (1954). Successful surgical therapy was reported by Barrett and Hickie (1957) in a 17-year-old boy.

The author has observed two cases of cor triatriatum in which the *accessory left atrium com-*

municated not only with the left atrium but with the right atrium (Figure VI-156). If the accessory chamber is a common pulmonary vein, then the opening with the right atrium is to be considered an anomalous connection (Edwards and Helmholtz, 1956).

The functional derangement in such cases is comparable to that usually given for the Littenbach syndrome. The obstruction, in the pathway leading to the left side of the heart, and the additional opening produces a left-to-right shunt. In descriptions of other cases which have



Figure VI-157. Case of stenosis of each of the four pulmonary veins in a 1-year-old boy. *a*, Left side of left atrium (L.A.). Orifice (circle) of unopened left upper pulmonary vein (L.V.) is markedly stenotic. The left lower pulmonary vein (L.L.) has been opened. Between the arrows is shown the rough lining of the stenotic zone. *b*, Section through stenotic area of one of the pulmonary veins. Nonspecific fibrous intimal thickening of main channel and of a tributary vein. (Elastic tissue stain; X 300.)

come to the attention of the author, the above arrangement was associated with an atrial septal defect which joined the right atrium and the true left atrium. In this circumstance, all or part of the pulmonary venous blood shunted to the right atrium could be redirected to the left atrium through the atrial septal defect. Blood flowing through this channel would inevitably be partly systemic venous in nature. While, in the known cases of cor triatriatum with anomalous connection of pulmonary veins, the anomalous connection has been with the right atrium, it is theoretically possible in cor triatriatum to have anomalous pulmonary venous connection with a systemic vein.

Stenosis of Individual Pulmonary Veins

Stenosis of individual pulmonary veins is mentioned only occasionally in the literature (Emslie-Smith *et al.*, 1955; Andrews, 1957). In pure form, all of the pulmonary veins connect with the left atrium, yet one, several, or all may be stenotic. The basis for the lesion

is intimal fibrous proliferation. The functional derangements depend on the severity and distribution of the obstruction.

The author examined the heart of a boy 1 year of age, in which each of the 4 pulmonary venous orifices at the left atrium was so stenotic as to admit only the finest probe (Figure VI-157). An atrial septal defect was also present.

When pulmonary venous obstruction exists in the absence of anomalous connection, the question might logically be raised whether the obstructing lesion is congenital or acquired. The author's opinion that these lesions are congenital is supported by the association of other congenital defects in cases of lesions of this sort and by the association of anomalous pulmonary venous connections in some instances of stenosis of pulmonary veins. The latter situation would indicate that the obstruction to the normal route had occurred early enough so that primitive connections still existed between the pulmonary vascular bed and systemic veins. Moreover, this phenomenon may occur so early that evidently the vas-

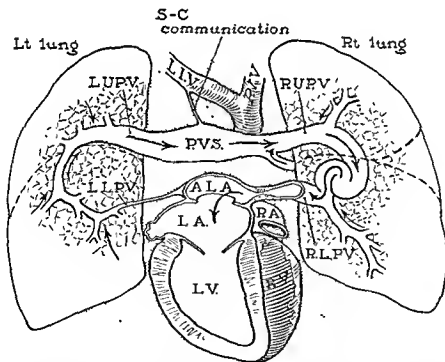


Figure VI-158. Congenital stenosis of individual pulmonary veins with anomalous connection of pulmonary veins. Heart and lungs viewed from behind. (L.U.P.V. and L.L.P.V. indicate left upper and left lower pulmonary veins; P.V.S., pulmonary venous sinus; A.L.A., accessory left atrium; L.L.V. and R.L.V., left and right innominate veins; S-C communication, narrow communication representing an embryonic connection with the splanchnic plexus and the cardinal system.) Case of Becu and associates (1955). (Reproduced with permission of A.M.A. Archives of Pathology.)

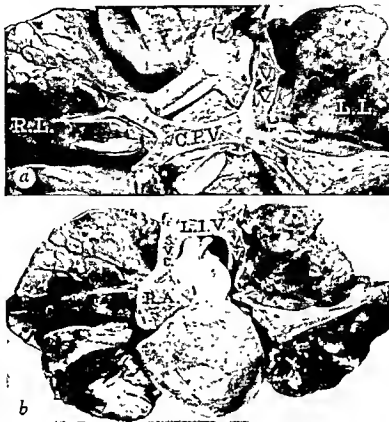


Figure VI-159 Total anomalous pulmonary venous connection to left innominate vein. *a* The heart has been reflected upward. The lungs are viewed from in front. The veins of the right lung (R.L.) converge behind the heart with the veins from the left lung (L.L.) to form a single structure termed the "common pulmonary vein" (C.P.V.). From the left upper aspect of the latter, an anomalous vertical vein (V.V.) ascends in front of the left pulmonary hilus. *b* The vertical anomalous pulmonary vein has joined the left innominate vein (L.I.V.) from which blood is carried into the superior vena cava (S.V.C.) and ultimately into the right atrium (R.A.). Cases of this type have frequently been classified as anomalous connection of the pulmonary veins with a persistent left superior vena cava. Since no communication with the coronary sinus exists, the anomalous vein should not be regarded as a persistent left superior vena cava.

cular bed of the individual lobes may still not be perfectly developed. This belief is supported by the case of Becu and associates (1955) which had extensive occlusive lesions of the major pulmonary veins with compensating anastomotic connections between the veins of the various pulmonary lobes (Figure VI-158). Ultimately, in spite of the extensive anomalous connection within and across the lungs, the blood was delivered to the left atrium.

Total Anomalous Pulmonary Venous Connection

PATHOLOGIC ANATOMY

By definition, total anomalous venous con-

nection of the pulmonary veins has no communication with the left atrium, all the pulmonary venous blood being carried into the right atrium directly or into one of its tributary veins. When all of the pulmonary veins join the right atrium or a tributary vein, there are two types of anatomic features of the pulmonary venous system. Either a simple junction of veins without formation of a chamberlike structure may exist, or the veins may converge into a sinus or chamber. Loeffler classified the latter arrangement as a form of *cor triatriatum*. (See *Cor Triatriatum*, page 484.) Regardless of the specific type of convergence of the pulmonary veins, a venous

channel runs to the site of connection with the systemic venous system or the right atrium. In any event, the pulmonary veins do not perforate the pericardium and usually converge posterior to it.

A number of reviews on the pathologic and clinical features have been presented (Brody, 1942; Snellen and Albers, 1952; Keith *et al.*, 1954; Sepulveda *et al.*, 1955; Cott *et al.*, 1956; Darling *et al.*, 1957). In a review by Burroughs and the author (1958), 188 cases of total anomalous connection of the pulmonary veins were found in the literature and in the material of the Mayo Clinic. Of these, 66 had associated major intracardiac malformations, including cor biloculare, cor triloculare biatriatum, persistent truncus arteriosus, complete transposition of the great vessels, pulmonary stenosis or atresia, coarctation of the aorta, and anomalous connection of the systemic veins, or the complex of intracardiac malformations was associated with agenesis of the spleen. No data as to the presence or absence of intracardiac malformations were given in 3 cases, but in 119 cases no major intracardiac malformations existed in association with total anomalous pulmonary venous connection.

Common sites of anomalous connection of pulmonary veins are the left innominate vein (Figure VI-159), the coronary sinus, a superior vena cava, and the right atrium. Less often, a common anomalous pulmonary vein descends and perforates the diaphragm, usually in association with the esophagus, to terminate in the ductus venosus (Figure VI-160), left portal vein, or left gastric vein. In some instances, as in the case of Butler (1952b) the vein enters the abdomen through an accessory orifice in the diaphragm between the inferior vena cava and the esophagus to join the portal system. In other cases the inferior vena cava or a hepatic vein is joined.

Usually, there is one site for termination of the entire anomalous pulmonary venous system. In 8 cases found by Burroughs and Edwards in which no cardiac malformation existed, the anomalous pulmonary venous connections were at multiple sites. The following combinations of multiple anomalous pulmonary venous terminations existed: azygos and portal vein; right atrium and left innominate vein; superior vena cava and left innominate vein; superior vena cava and right atrium; coronary sinus and right atrium; inferior vena cava and left innominate vein.

One particular type of connection deserves

special mention because it is relatively common, and it has been incorrectly called "persistent left superior vena cava" (Gardner and Oram, 1953, and others). In this connection, all the pulmonary venous blood is carried to a vein that runs vertically, usually anterior to the aortic arch and terminates in the beginning of the left innominate vein (Figure VI-159). This structure does not make junction with the heart. A true persistent left superior vena cava represents the left anterior cardinal vein of the embryo and, characteristically communicated with the heart to become the coronary sinus at its proximal end. In the absence of a connection with the heart, the vertical vein which receives all of the pulmo-

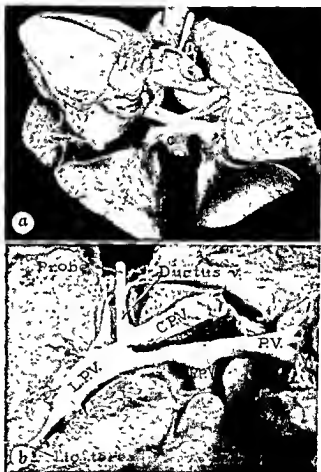


Figure VI-160. Total anomalous pulmonary venous connection into the ductus venosus. The second patient of Edwards and DuShane (1950), a male 6 days old (Reproduced by permission of *Archives of Pathology*.) *a* Ventral view of the lungs. The heart has been displaced to the right. A common pulmonary vein (C.P.V.) is formed by union of four pulmonary veins. The common vein lies ventral to the esophagus and descended through the diaphragm into the abdomen. *b* The common pulmonary vein (C.P.V.) inserts into the narrow ductus venosus (Ductus v.). P.V. indicates portal vein; R.P.V., right portal vein; L.P.V., left portal vein.

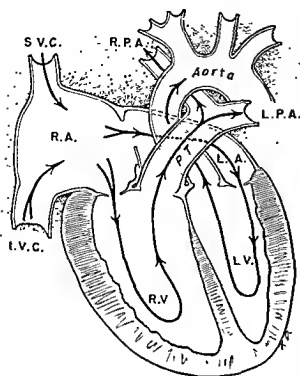


Figure VI-161. The intracardiac circulation in complete anomalous drainage of the pulmonary veins. (From Edwards and DuShane, 1950. Reproduced by permission of *Archives of Pathology*.)

nary veins cannot be regarded as a persistent left superior vena cava. On developmental grounds, it may represent a persistent left superior vena cava, which has lost its connection with the coronary sinus. However, it more probably represents a separate persisting channel. This vein should be designated by some term other than "persistent left superior vena cava," possibly "vertical anomalous pulmonary vein" (Edwards and Helmholtz, 1956).

The over-all size of the heart is larger than normal. Characteristically, the right atrial and ventricular chambers are enlarged and the right ventricular wall, additionally, is frequently hypertrophied. The left atrium and ventricle are small, certainly by comparison with the right-sided chambers. There may be an absolute reduction in size but this is not universal. An interatrial communication exists. Usually this is situated at the fossa ovalis and takes the form either of a valvular competent foramen ovale or a true atrial septal defect.

FUNCTIONAL AND CLINICAL FEATURES

If there are no major intracardiac malformations, all the incoming blood is pooled

in the right atrium, and bidirectional shunts exist. The left atrium receives its blood through the interatrial communication (Figure VI-161). Theoretically, it is possible for the systemic and pulmonary arterial blood to have equal saturation with oxygen and this does occur on occasion (Swan *et al.*, 1956). In other instances, minor differences exist in saturation between the blood of the two arterial systems. These serve to distinguish total anomalous pulmonary venous connection from common atrium. The differences in saturation depend on the site of the anomalous pulmonary venous connection. There is a difference in transatrial shunting of blood returning from the inferior vena cava contrasted to that coming from the superior vena cava. Preferential shunting from the inferior vena cava exists (Swan *et al.*, 1956). Thus, among patients having anomalous connection of the pulmonary veins to the superior vena cava, it is likely that the pulmonary arterial blood would be more highly saturated than the systemic arterial blood. Conversely, in patients having an anomalous connection to the inferior caval system the oxygen saturation of the systemic arterial blood would be expected to be somewhat higher than that of the pulmonary arterial blood.

The outward appearances of patients with total anomalous pulmonary venous connection varies considerably, some are cyanotic and others are not cyanotic, even though they have some degree of arterial desaturation (DuShane, 1956). The clinical picture in total anomalous pulmonary venous connection appears to depend upon the size of the interatrial communication and the presence or absence of venous obstruction (Burchell, 1956). These factors influence total pulmonary blood flow which is the main feature determining the ultimate saturation of the systemic arterial blood. The systemic blood is more highly desaturated in patients having a low pulmonary flow than in patients having a large pulmonary flow. Swan and associates (1956) found that reduced pulmonary blood flow was always associated with increased pulmonary arterial pressure. They concluded that a reduction in the oxygen saturation of systemic arterial blood is associated with increased pulmonary vascular resistance. One source for the high resistance,

when present, may reside in the anomalous pulmonary vein.

As the clinical picture varies, so may the *roentgenographic features* (Bruwer, 1956). Characteristic for total anomalous pulmonary venous connection to the left innominate vein (Snellen and Albers, 1952) are the engorged pulmonary fields and, when present, a figure-of-eight pattern which includes the shadow of the heart and the area above it. Some patients have a nonspecific cardiac enlargement with evidence of decreased pulmonary flow. This picture is seen particularly in patients who have difficulty in the early weeks after birth. Among patients who survive to adult life with high pulmonary blood flows, the roentgenographic picture may be impossible to distinguish from that in atrial septal defect or other malformations associated with high pulmonary flow.

Methods have been devised for surgical correction of total anomalous pulmonary venous connection (Burrroughs and Kirklin, 1956).

CONNECTION BETWEEN LEFT ATRIUM AND A SYSTEMIC VEIN

Except for connection with the left superior vena cava or the coronary sinus, this

type is rare (McIntosh, 1926; Harris, *et al.*, 1927; Edwards and DuShane, 1950, Figure VI-162). The anomalous vessel arises from the dorsal aspect of the left atrium near the entrance of one of the pulmonary veins. It then ascends dorsal to the bronchus and the pulmonary artery of the side on which it originates.

In McIntosh's case the systemic vein that connected with the anomalous vessel was the superior vena cava, in the case of Harris and associates, the right internal jugular vein; and in the case of Edwards and DuShane, the left innominate vein (Figure VI-88b). Since each of the systemic veins into which the anomalous vessel inserts is a derivative of the cardinal system, the name "levoatriocardinal vein" has been suggested for this structure (Edwards and DuShane, 1950). The structure probably represents a form of anomalous pulmonary venous connection in which the part of the pulmonary venous system participating has been incorporated by differential growth into the left atrium. In the cases of McIntosh and of Edwards and DuShane the levoatriocardinal vein was of functional significance because of associated mitral atresia and

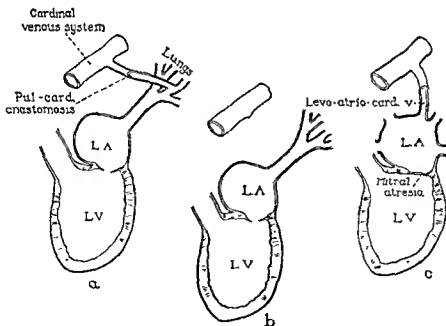


Figure VI-162. The developmental basis for formation of a levoatriocardinal vein. *a*. Communication between a pulmonary vein and a representative of the cardinal venous system. This is normal at an early stage of development. Later, as represented in *b*, the communication disappears. If it is retained, the communication is carried into the dorsal wall of the left atrium along with the pulmonary vein to which it is attached (see *c*). (From Edwards and DuShane, 1950. Reproduced by permission of *Archives of Pathology*.)

premature closure of the foramen ovale. The levoatriocardinal vein represented the only effective outlet for blood coming to the left atrium from the lungs. One case (Harris *et al.*, 1927) had complete transposition of the great vessels. The anomalous venous channel was probably of some beneficial influence as an additional communication between the two circulations.

Partial Anomalous Pulmonary Venous Connection

PATHOLOGIC ANATOMY

In partial anomalous connection of the pulmonary veins, as the term implies, some of the pulmonary veins connect normally with the left atrium while the remainder join a systemic vein or the right atrium. Usually only one lung or part of it contributes to the anomaly, anomalies of the right pulmonary veins being about six times as common as anomalous connection of the veins of the left lung (Hickie *et al.*, 1956).

In rare cases (Hwang *et al.*, 1950, Ellis *et al.*, 1958), veins of both lungs are anomalously connected while only a small segment of the pulmonary venous system connects with the left atrium. These cases form a group somewhat different from that of the usual example of partial anomalous pulmonary venous connection. Functionally they are more akin to total anomalous connection. An alternate classification for these cases might be *subtotal anomalous pulmonary venous connection*.

The usual examples of partial anomalous pulmonary venous connection form three more or less well-defined pathologic entities. Anomalous connection of left pulmonary veins may involve the entire left lung or only the upper lobe of the left lung. Usually the left innominate vein receives the anomalous channel represented by a solitary vessel which passes anterior to the left pulmonary hilus (Geraci and Kirklin, 1953, Hickie *et al.*, 1956, Zion, 1956). Rarely the anomalous vein terminates in the coronary sinus. An atrial septal defect at the fossa ovalis is usually associated. In a rare case (Hickie *et al.*, 1956) the atrial septum is intact.

Anomalous connection of right pulmonary veins takes two forms. In the more frequent form (representing the most common type of partial anomalous connection), the anomalous

vein or veins from the right lung join either the superior vena cava or the right atrium or both. An atrial septal defect involving the area superior to the fossa ovalis is usually present. Cases of this type have been discussed more fully in the section dealing with Interatrial Communications (page 269). The second form of anomalous connection involves all or part of the right lung, and the anomalous vein perforates the diaphragm to join the inferior vena cava (Dotter *et al.*, 1949; Cooke *et al.*, 1951; McKusick and Cooley, 1955). Anomalous arterial supply by a branch from the aorta to the lower lobe of the right lung may be associated (Cooke *et al.*, 1951). Partial sequestration or bronchial agenesis may be present in the right lung (Findlay and Maier, 1951; Bruwer, 1953).

FUNCTIONAL AND CLINICAL FEATURES

The effect upon the heart of partial anomalous drainage of the pulmonary veins resembles that of atrial septal defect. This includes dilatation of the right atrium and dilatation and hypertrophy of the right ventricle. The pulmonary trunk and the other pulmonary vessels may be dilated. These features may be demonstrated roentgenographically.

In rare instances, as in two of the cases of Grishman and associates (1949), the anomalous vein itself may cast a shadow in the roentgenogram. It is difficult or impossible to make the clinical diagnosis of partial anomalous drainage of the pulmonary veins without special studies. On cardiac catheterization, the right atrial blood has an abnormally high concentration of oxygen. This condition may, of course, be the result of an atrial septal defect without other malformations.

If the catheter is passed directly into an anomalous vein, and it is demonstrated that the blood is completely saturated with oxygen, the findings can be considered diagnostic for anomalous drainage of a pulmonary vein (Knutson *et al.*, 1950). Even under these circumstances, it may be impossible to rule out an associated atrial septal defect (Courmand *et al.*, 1949), since the catheter may pass through an atrial septal defect or even a valvular competent patent foramen ovale, enter the left atrium and then a normally connecting pulmonary vein (Edwards *et al.*, 1953).

Swan and associates (1953) have established criteria for distinguishing partial anomalous pulmonary venous connection from atrial septal defect by the use of dye-dilution techniques. The patient is not likely to be disabled unless more than 50 per cent of the blood leaving the lungs enters the right side of the heart (Brody, 1942).

Pulmonary Arteriovenous Fistula

Congenital pulmonary arteriovenous fistula, also called *arteriovenous aneurysm and cavernous hemangioma of the lung*, was reviewed extensively by Ciampalmo (1950). The lesion is usually confined to one pulmonary lobe. In the patient of Sisson and associates (1945), however, fistulas were found in both lungs at necropsy. In the usual case, part or all of a lobe is replaced by a plexus of various-sized tortuous vessels which intercommunicate. The condition is important because it allows pulmonary arterial blood to pass to the pulmonary veins and so to the left side of the heart without oxygenation in the lungs. As a result, there is desaturation of the systemic arterial blood. Cyanosis and the other features of hypoxia may appear, including weakness, fainting, polycythemia and clubbing of the fingers and toes (Goldman, 1943), but in milder cases cyanosis is not apparent (Freedman *et al.*, 1952). It was believed for many years that some of the patients had had severe cardiac malformations (Baer *et al.*, 1950; Husson, 1956). The lesion, however, may be visualized on roentgenographic examination (Smith and Horton, 1939; Makler and Zion, 1946; Grishman *et al.*, 1949; Steinberg and McClenahan, 1955), and cure may be effected

by resection of the involved pulmonary lobe (Hepburn and Dauphinee, 1942; Jones and Thompson, 1944; Burchell and Clagett, 1947; Maier *et al.*, 1948; Wodehouse, 1948) or of the individual lesions when they are multiple (Janes, 1944).

Since the blood which flows through the anomalous communication is venous blood which bypasses normal pulmonary tissue, *cerebral abscess* may develop as a complication of congenital pulmonary arteriovenous fistula, as it may in those types of congenital cardiac disease which are characterized by veno-arterial shunts. Such a complication was reported by Wodehouse (1948) in a boy aged 13 years with a pulmonary arteriovenous fistula. Necropsy revealed no intravascular focus of infection. *Bacterial infection of the fistula* is another complication which might be anticipated. This has been described by Maier and associates (1948). The patient was a woman aged 20 years who was cured both of the fistula and of the infection by excision of the involved lobe. Patients with congenital arteriovenous fistula of the lung, frequently have associated *familial telangiectasia* (Rendu-Osler-Weber disease) (Goldman, 1948; Armentrout and Underwood, 1950).

Rarely a pulmonary artery connects with the superior aspect of the left atrium (Friedlich *et al.*, 1950; Mack and McNie, 1953). In such instances, a right-to-left shunt is possible through this connection. Developmentally these cases should be regarded as examples of total anomalous pulmonary arteriovenous fistula between a pulmonary artery and the common pulmonary vein, the fistula being retained while the common pulmonary vein is carried into the left atrium.

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Degenerative Lesions

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POSTMORTEM CHANGES

Rigor mortis involves the heart earlier than the skeletal muscle, starting within one hour after death. The left ventricle is the first portion of the heart to be involved. Aschoff (1919) believed this to be the reason why the left ventricle, after death, contains prac-

tically no blood while the right ventricle is still partly filled. Most of the liquid blood is found in the right atrium. In some hearts with severe degenerative changes of the myocardium, rigor mortis does not occur. After 12 to 24 hours, rigor mortis disappears

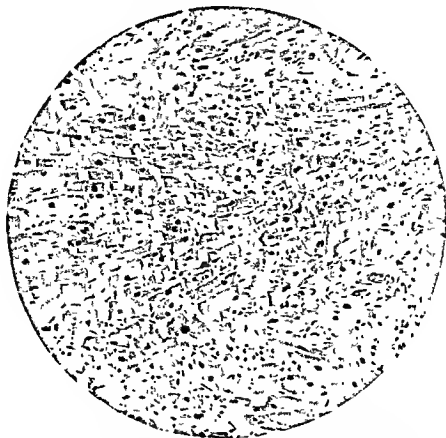


Figure VII-1. Segmentation of cardiac muscle fibers. Death was caused by lobar pneumonia. Autopsy was performed 70 hours after death. (WCGH, 42 A 54.)

and the consistency of the heart becomes very soft; the *myocardium* becomes more and more parboiled in appearance, its normal architecture increasingly obscured, and the papillary muscles and columnae carneae flattened. About 24 hours after death, and sooner if the body is not refrigerated, the endocardium becomes gradually stained with decomposed hemoglobin and assumes a red color. This is particularly noticeable in the valvular endocardium. Later, the hemoglobin becomes similarly diffused into the myocardium and pericardium. While putrefaction occurs, bubbles of gas may be found in the cardiac chambers, particularly in the right atrium.

Few studies have been made of autolysis of the myocardium. In dogs, Yokoyama and associates (1955) found a progressive loss of stainable glycogen, the sequence of changes being similar to that seen in experimental ischemic injury. One hour after the onset of autolysis there was patchy loss of the glycogen, and after 5

hours, no stainable glycogen remained. The lipochrome pigment was unaltered during autolysis and no other stainable fat had accumulated.

Blood clots commonly form in the heart chambers after death and may be confused with ante-mortem thrombi. Compared to thrombi, the clots of coagulated blood are soft, are either dark red or yellow-white (resembling chicken-fat), with varying amounts of fibrin loosely attached to the endocardium. They are commonly found in the atria, and especially within the auricular appendages and in the apical portion of the ventricles. They may be attached by strands between the pectinate muscles of the auricular appendages. Clots are easily removed with forceps or by a stream of water. They also often extend into the great vessels or from one cavity into an adjacent cavity. Characteristically they are smooth and elastic.

Thrombi are drier than clots, are not elastic and are easily torn when an attempt is made to remove them. They are not as

smooth and glistening as clots, and are attached to the underlying endocardium. If a thrombus has been present for some time, the portion nearest the endocardium may be partially organized while the bulk of the thrombus may show softening and laminar depigmentation.

Segmentation and Fragmentation of Myocardium. Segmentation is usually described as separation of the myocardial muscle fibers in the line of the intercalated disks (Figure VII-1) and fragmentation as fracture of the fibers at some point between the disks.

The older pathologists thought that segmentation and fragmentation were two distinct conditions sometimes occurring during life, and regarded them as a cause of death. (See Hektoen, 1897, and Saphir and Karsner, 1924, for older literature.) They believed that, if the ruptured ends of the muscle fibers were straight, it signified that the rupture occurred in the line of the intercalated disk. This process was called segmentation. However, if the ruptured ends were irregular or combshaped (pectinate) it was thought that the line of fracture went through the myocardial fibers between the disks. This process was called fragmentation. Jordan and Bardin (1913) found that the intercalated disks in hypertrophic hearts were not arranged as straight lines but were irregular and shaped like the teeth of a comb. It then became clear that segmentation and

fragmentation are essentially the same process (Saphir and Karsner, 1924).

In experiments designed to produce severe dilatation of the heart, Saphir and Karsner showed that prior to rupture of the myocardial fibers, the intercalated disks appeared to be prominent. It also seems likely that fracture of muscle fibers which is definitely not in relation to the intercalated disks must be regarded as an artefact caused by the microtome knife. In such instances it can often be demonstrated that the lines of fracture also pass through the muscle nuclei. Hamperl (1929) believed that fragmentation in the human heart does not occur before onset of rigor mortis and that the points of rupture have some sort of relationship to more severely contracted muscle fibers. He was unable to produce fragmentation in the experimental animal. However, he did not mention the state of the intercalated disks or the relationship between the intercalated disks and the points of rupture.

Saphir (1933) paid special attention to the intercalated disks in human hearts. While in sections of non-dilated hearts, stained with hematoxylin and eosin, the intercalated disks were hardly noticeable, in sections of dilated hearts they were prominent and easily discernible. They were more pronounced in the muscle fibers situated close to the endocardium than in those close to the epicardium. The presence of dilatation of the heart was often indicated by the microscopic appearance of prominent intercalated disks, and this deduction was often confirmed by reference to the gross description of flattened papillary muscles and columnae carneae.

DISTURBANCES OF METABOLISM

Disturbances of Protein Metabolism

Cloudy Swelling and Hydropic Degeneration. The heart may show little change on gross examination; it may at most be slightly enlarged, with opaque and granular cut surfaces, an appearance which is described as parboiled. Microscopically the cells are swollen and the cytoplasm is granular and indistinct. Frequently the nucleus is partly obscured. In hydropic degeneration small droplets accumulate in the cytoplasm (Figures VII-2 and VII-3).

In hydropic degeneration (Figures VII-2 to 4) small acidophilic droplets appear in

the sarcoplasm of the muscle fibers. Grossly this condition is indistinguishable from cloudy swelling. The nature of the changes in cloudy swelling and hydropic degeneration is not clear and probably is not the same in all cases. The swelling is attributed to increased imbibition of water resulting from a change in osmotic pressure, so that the cells hold more fluid within the sarcoplasm. The granules in the sarcoplasm are presumably protein in nature.

Lucké and McCutcheon (1926) have shown experimentally that two types of cellular swelling may occur in the eggs of the sea urchin. The first



Figure VII-2. Hydropic degeneration of myocardium in heat stroke. Death 96 hours after onset of illness X240. (Courtesy, Armed Forces Institute of Pathology, Acc. 95093, Neg. 88408.)

type of swelling occurs when the osmotic pressure of the outside solution is lowered. Such swelling is reversible, when the cause is removed, the cells return to normal. The second type of swelling is induced by various injurious agents such as acid, ether and heat. This type of swelling is irreversible and the cells are killed. It is not known whether these results are applicable to human beings, but they suggest that cloudy swelling may not always be reversible and sometimes may be associated with death of the cells.

Experimental findings in animals indicate that cloudy swelling is a reflection of mitochondrial injury. Thus it has been shown that, following toxic injury, the mitochondria in the liver and elsewhere swell and assume a spherical rather than an oblong form coincidentally with the appearance of cloudy swelling (Gansler and Rouiller, 1956). The work of Fonnesu and Severi (1956) suggests that cloudy swelling represents the morphologic equivalent of the uncoupling between oxidation and phosphorylation in the mitochondria.

A peculiar degenerative vacuolation (vacuolar infiltration, sarcolytic myocardiosis, myocytolysis) is sometimes observed around infarcts (Schlesinger and Reiner, 1955), in anoxia, infections,

idiopathic cardiomegaly and beriberi (Wenkebach, 1934). It occurs in both the contractile myocardium and the fibers of the conducting system and may be particularly marked in the neighborhood of infarcts in the atria of the heart (Cushing *et al.*, 1942). Characteristically the lesions are focal, small, and have ragged borders. The sarcolemmal sheaths are often empty or contain a few frayed or fragmented fibrils and small amounts of protein precipitate. The nuclei may be large, irregular and deeply stained, and some contain small, clear vacuoles. Similar lesions occur in potassium deficiency (see below). The nature of the intracellular material is not clear. In experiments on myocardial infarction in dogs, we have observed similar changes in the myocardial fibers abutting on the infarct and have been able to show that the material is glycogen. The pathogenesis of the lesion is not known. Experimentally, degenerative vacuolation has been produced in cats by anoxia, in rabbits by injections of adrenaline or by hyperthyroidism, and in rats by feeding diets deficient in vitamin B and protein.

Mucinous or Basophilic Degeneration. This is a focal lesion characterized by increased cytoplasmic basophilia of myocardial fibers. Scotti (1955) found such a degenerative change in 53 of 75 hearts, but other authors

have reported a lower incidence (Doerr, 1952). All chambers of the heart may be affected, but the left ventricle is most frequently involved. Mucinous degeneration has been observed at all ages. Although the cause is unknown, some authors have thought it was related to myxedema or anoxia. The available evidence indicates that uremia and anemia are not related to the lesion. The affected fibers are sharply outlined, the cytoplasm swollen with basophilic substance, and the nuclei usually are unaffected, although occasionally they are pyknotic. In the early stages the basophilic substance is pale, indistinct, and separates the myofibrils without fragmenting them. The material accumulates first around the nucleus and then spreads through the cell replacing the myofibrils. Finally, only a thin rim of muscle may remain at the periphery while fragments of fibrils and vacuoles are scattered through the cell. Histochemical studies show that the basophilic substance exhibits metachromasia with toluidine blue, reacts positively with the periodic acid-Schiff reagent even after diastase digestion, and stains light red with Mayer's

mucicarmin. It gives a negative Feulgen reaction and ribonuclease test, and cannot be stained by von Kossa's method. Thus the basophilic material is probably a mucoprotein or acid mucopolysaccharide and is not related to desoxyribonucleic or ribonucleic acids.

Myocardosis. Rarely the interstitial tissues of the myocardium become infiltrated with edema fluid which is rich in proteins and shows an affinity for basophilic stains. In sections stained with hematoxylin and eosin, the material appears homogeneous and is focally distributed in the myocardium and endocardium, especially in the right side of the heart. It is said to be present chiefly in aged patients with senile thoracic rigidity (Selburg, 1955).

Hyaline Degeneration. The recognition of hyaline degeneration cannot be made grossly but must await microscopic analysis. It is seldom diffuse but often localized. It may appear in the form of small acidophilic droplets within the sarcoplasm of the muscle fibers or, when diffuse, replace the muscle fibers. It is probable that this represents



Figure VII-3. Hydropic degeneration of myocardium. Same case as that of Figure VII-2. (Courtesy, Armed Forces Institute of Pathology, Acc. 95093-2, Neg. 88410.)

coagulation of sarcoplasmic protein which occurs as the fiber dies. An interesting change sometimes occurs in older myocardial infarcts in which dead muscle fibers are not replaced by scar tissue but gradually become hyalinized. One may encounter areas in the myocardium which at first glance appear to be normal, in which the muscle fibers show increased eosinophilic staining and have no nuclei. Since the general shape of these fibers is preserved, the term "mummification" may be used for this type of hyalinization. Whether Zenker's (waxy) degeneration occurs in the myocardium is questionable.

AMYLOIDOSIS

Amyloidosis. An abnormal protein complex called *amyloid* may be deposited in certain tissues of the body. Amyloidosis is usually classified as (1) primary, (2) secondary; (3) amyloidosis associated with multiple myeloma; and (4) localized amyloidosis of the heart, larynx, skin, bladder or other organ. The most common form is secondary amyloidosis which is ordinarily preceded by chronic suppurative disease or less frequently by nonsuppurative chronic inflammation. Primary amyloidosis and localized amyloidosis occur spontaneously without known cause.

Primary Amyloidosis of Heart. *Criteria for diagnosis.* The criteria for the diagnosis of primary amyloidosis are given by Hartney and associates (1949). In the order of importance, they are: (1) absence of a predisposing factor, such as chronic suppuration; (2) failure of the amyloid deposits to show the usual staining reactions for amyloid (the response to dilute Lugol's solution and sulfuric acid, congo red and crystal violet may be irregular and capricious in primary amyloidosis); (3) non-involvement of organs commonly affected in secondary amyloidosis; and (4) deposits in unusual sites such as the heart, blood vessels, skin and skeletal muscle.

Incidence. Primary amyloidosis is frequently accompanied by cardiac involvement.

Lindsay (1946) studied 43 cases at autopsy. Cardiac involvement was present in 39, in 32 of which clinical signs of heart failure were evident

during life. In an analysis of 130 published cases of primary amyloidosis and 15 personally studied cases, Symmers (1956a) reported involvement of the heart in 90 per cent. Jones and Frazier (1950) also observed a high incidence among patients in West Tennessee—2.3 per cent of 600 consecutive autopsies of adults.

Sites of involvement. The *pericardium* and *epicardium* are frequently involved in amyloidosis, the involvement being either nodular or diffuse. In the nodular form the deposits may be few or many and may vary from 1 mm. to 4 cm. in diameter. The nodules are usually pearly gray and translucent, and occasionally yellow-gray; they are common in the ventricular wall. Sometimes the deposits form furrows. In the diffuse type of amyloidosis the epicardium and pericardium are thick, gray-yellow and semitranslucent. Rarely there is a gray-gold, gelatinous membrane on the surface. Microscopically the blood vessels of the pericardium, as well as of the interstitial tissues, are involved. Often rings of amyloid surround the fat cells of the pericardium (Mathews, 1954).

The *myocardium* is attacked more often than other parts of the heart. Both the atria and the ventricles may be either diffusely or focally affected. In diffuse involvement the atrial and ventricular walls are likely to be thick and leathery. Usually they are firm and pale gray-tan or brown and have a waxy, translucent, homogeneous appearance. The muscle cuts with increased resistance and, on opening the heart, the chambers do not collapse but retain their globular shape. Irregular translucent, pearly gray streaks or flecks may be scattered diffusely through the myocardium. The streaks, particularly in the region of the pericardial sinus, often have a peculiar parallel arrangement or are sinuous. They also occur in the endocardium and pericardium and may extend deeply into underlying tissues, particularly in the atria where the full thickness of the myocardium may be involved. Microscopically there are two types of involvement, both of which follow a characteristic pattern. In the first type amyloid is found in blood vessels, including the main coronary arteries, arterioles, capillaries and veins.

In the second type there is diffuse interstitial infiltration of the myocardium. The myocardial fibers are compressed and undergo necrosis and atrophy, which may be extensive. When atrophy is present the sarcoplasm is vacuolated and contains deposits of lipid or pigment, and nuclear degeneration and necrosis are common. With excessive deposition, the muscle cells disappear entirely, leaving empty amyloid rings or solid sheets of amyloid. Fragmentation of myocardial fibers is frequent.

According to some observers, the amyloid is deposited in and about altered reticulum (Jones and Frazier, 1950). Teilum (1956) has presented evidence that the reticuloendothelial cells, containing polysaccharide substances colored by the periodic acid-Schiff technique, may be directly concerned with the synthesis of amyloid and related substances. According to Peters (1943), amyloid is first deposited on the cell membrane; gradually the deposits increase, giving rise to the distinctive pericellular rings, and the tissues undergo atrophy because of pressure and inanition. Finally, even the fibrous skeleton may disappear without trace. In heavily affected areas, the appearances may resemble a fresh infarct. In addition to the usual interstitial deposits, amyloid may rarely be found within the sarcoplasm of the myocardial fibers as a fine linear deposit in relation to the myofibrils. Fusion of the deposits may greatly distend the cells. Sometimes giant cells may contain amyloid infiltrate in affected areas. Amyloid nodules may show a laminar structure and may undergo calcification and even ossification.

Gross infarction of the myocardium may occur as a result of obstruction of a coronary artery by a nodular deposit of amyloid. In one case observed by Symmers (1956b), the left ventricle had ruptured through a massively infiltrated area and the patient died of hemopericardium. Often the heart is considerably enlarged, weighing as much as 600 grams.

The mural endocardium is infiltrated in a majority of the recorded cases, usually in the form of stratified or nodular deposits. Occasionally the infiltration is continuous with the amyloid in the myocardium.

In 16 of 43 cases of primary systemic amyloidosis reported by Lindsay (1946) amyloid deposits were present in the heart valves. The valvular involvement is usually slight and may only be demonstrable in microscopic sections. A few cases, however, have discrete nodules on the valves measuring from 1 to 3 mm. The amyloid occurs in either the cusp or the annulus of the valve. Sometimes the involvement is diffuse, leading to stiff thick cusps and stenotic orifices. In still other cases the thickening is plaque-like, and occasionally very large nodules are found. All 4 valves are reported to be involved with about equal frequency. Frequently, the amyloid extends from the ring of the valve to its free edge. Amyloid may also lie in the deeper layers of the valvular and mural endocardium.

The *chordae tendineae* may be involved in the amyloid infiltration. Usually the amyloid originates in the valvular endocardium and extends into the substance of the chordae tendineae.

As stated above, the coronary arteries may be so extensively involved as to produce occlusion and myocardial infarction. Although the large coronary arteries may be affected, it is more usual to find the medium-sized and small arteries involved. The arterioles, capillaries and veins have also been reported as sites of amyloid infiltration.

Clinical manifestations. Signs of cardiac insufficiency constitute the most important clinical feature of primary amyloidosis. The patients generally are about 50 years of age or older, usually have not had evidence of previous hypertension, and gradually develop cardiac failure, cardiac enlargement and paresthesias. The response to digitalis and other forms of treatment is poor and death occurs several years after the onset of symptoms. The failure may be produced in a variety of ways. Deposits may form in the valves of the heart and cause stenosis or insufficiency. The material may infiltrate the interstitial tissues of the myocardium, endocardium or pericardium. When the coronary arteries are affected, stenosis or occlusion may result, with consequent angina pectoris or myocardial infarction. It is also recognized that extensive deposits of amyloid in the vessels and alveolar walls of the lungs may lead to

hypertrophy of the heart, especially of the right ventricle and atrium. Electrocardiographic findings are variable and include low voltage of the QRS complexes and flattening or inversion of T waves. Studies by cardiac catheterization confirm the clinical impression that amyloidosis strikingly resembles constrictive pericarditis, because of the inelasticity of the amyloid myocardium which interferes with diastolic expansion of the heart (Gunnar *et al.*, 1955).

Amyloid Localized in the Heart. King (1948) and Dahlin and Edwards (1949) have described cases in which localized deposits of amyloid were found in the heart and in no other organs.

All of their patients were relatively old, ranging in age from 63 to 100 years. In most of the cases the amyloid could be recognized grossly, particularly beneath the endocardium of the atria. The deposits were minute, translucent and pink-gray. Both atria were involved with equal frequency. The right atrium near the mouth of the coronary sinus and the intima of the coronary sinus for a distance of about 2 cm. were the most common sites, whereas in the left atrium the regions most commonly involved were the posterior wall and septum. Microscopically the amyloid was discovered to be in the loose connective tissue in the atrial endocardium. In the myocardium it showed the same pattern as in primary amyloidosis. (See also Josselson *et al.*, 1952, Hüsselmann, 1955.)

Secondary Amyloidosis. The heart is usually spared in secondary amyloidosis. However, in exceptional cases small deposits of amyloid may be found. Thus, Huebschmann (1907) reported that in 8 of 9 consecutive autopsies on tuberculous patients with amyloidosis, amyloid was found in the heart also. Usually it is located in blood vessels, in the interstitial tissues of the myocardium or beneath the endocardium, and rarely in the valves or endocardium. In experimental amyloidosis, deposits occur commonly in the myocardium. In multiple myeloma the findings are usually similar to those in secondary amyloidosis, and involvement of the heart is slight. Less commonly, the distribution of amyloid is the same as in the primary form.

Staining Reactions of Amyloid. In sections stained with hematoxylin and eosin, amyloid has a homogeneous, amorphous character, staining pink, but usually not so brilliantly as collagen, and lacks the fibrillar nature of collagen. It exhibits metachromatic staining with certain basic dyes such as methyl violet and crystal violet, and stains light blue with aniline blue and methyl blue. With congo red it stains deep red. Amyloid assumes a yellow color with the van Gieson stain; rarely there is a slight pink cast, but never the bold red of collagen; this is a helpful characteristic in distinguishing deposits of amyloid from collagen. King has described the ability of amyloid to combine with ammoniacal silver without the use of any reducing agent and has devised a histochemical method based on this observation. Amyloid also is dimly fluorescent under ultraviolet light.

Gouty Heart. The heart may be affected in gout although actual tophi are rarely found. When they do occur, it is usually in the endocardium and the mitral valve. In order to make the diagnosis, positive identification of the presence of appreciable amounts of uric acid in the tophi is important, because small amounts of uric acid may be deposited directly from the blood upon previously existing deposits of phosphate and carbonate of lime.

Many of the cases reported in the literature fall into this latter category (Sodeman, 1941). However, Bunim and McEwen (1940) have reported an acceptable case of gouty tophi in the heart valves.

Traut and associates (1954), at necropsy of 2 patients who died of gout, demonstrated urates in the walls of the arteries and in the valves and muscle of the heart. In 1 case chalky deposits, which reacted positively to Weidel's test (murexide), were present on the undersurface of the mitral valve and extended over the parietal endocardium. In the other case urate crystals were present in the connective tissue of a coronary artery thickened by atherosclerosis. These authors recommend that tissues be fixed in absolute alcohol since aqueous fixatives dissolve the gouty deposits. Kaufmann (1929) mentions finding urate deposits in the pericardium.

Hypertension and hypertrophy of the heart

may result if there is accompanying renal disease. It is said that the incidence of hypertension and arteriosclerosis is higher in young gouty persons than in young persons suffering from other types of chronic disease. This increased incidence of hypertension and arteriosclerosis is less noteworthy in older age groups (Talbot, 1943).

Disturbances of Metabolism of Fat

Fatty Change in the Heart. Two varieties of fatty change occur in the heart: (1) fatty infiltration, which is an increase in subepicardial fat with infiltration and replacement of the myocardium by fat, and (2) fatty degeneration, which affects the sarcoplasm, and occasionally the nuclei, of the myocardial fibers. This classification is useful because there are clinical, pathologic and etiologic differences between the two conditions. Fatty infiltration "affects cells which normally contain fat and represents an alteration simply of the normal fat depots and transport"

(Saphir and Corrigan, 1933), whereas fatty degeneration is a deterioration of the myocardium caused by the action of some injurious agent, often a toxin, whereby fat or lipids accumulate in the myocardial cells.

Fatty Infiltration of Heart. Fatty infiltration means an excess in the deposit of normal fat and, therefore, is found in locations in which fat occurs normally. In the heart it is found in the subepicardium of the ventral wall of the right ventricle. Grossly the excess of fat is easily recognized on opening the right ventricle and atrium and exposing the tricuspid valve. In fatty infiltration there is also extension of the subepicardial fatty tissue into the myocardium with replacement of muscle fibers. Early fatty infiltration is seen here exclusively, and advanced infiltration is most marked in this location. Normally there is a sharp demarcation of the subepicardial fatty tissue from the myocardium. In fatty infiltration the fat extends somewhat like the cells of a malignant tu-



Figure VII-4. Myocytolysis of the myocardium adjacent to an infarct in the right atrium. Hematoxylin and eosin. X-400.

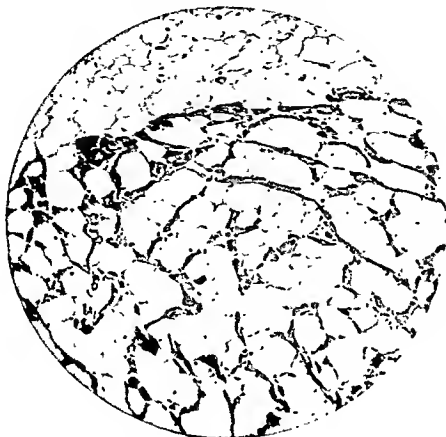


Figure VII-5. Fatty infiltration of right ventricle. X 175. (WCGH, 40 A 9.)

mor into the myocardium of the right ventricle and there is no clear-cut demarcation between the subepicardial fat and the myocardium. In this process, an excess of fat causes pressure atrophy and leads to disappearance of the muscle fibers and their replacement by fat. The process may continue until the entire myocardial tissue of the right ventricle in a certain area is replaced by fat. This may be noted particularly at the apex and, in advanced cases, just beneath the endocardium.

Fatty infiltration also may involve the left ventricle where it is seen best in the form of plaques or circumscribed areas just beneath the endocardium, covering the interventricular septum. Often it follows the course of the left bundle branch and its ramification. Since no extension of the subepicardial fatty tissue is demonstrable in these instances, it must be assumed that there is an excess of the minute amount of fat which may normally be present adjacent to these subendocardial fibers. Mönckeberg (1924) at-

tributed unexpected death to fatty infiltration of the bundle of His.

Microscopically, the excess of fat cells and the atrophy of muscle bundles and individual fibers, in the absence of any cellular infiltration (Figure VII-5), are easily demonstrable. It is also easy to discern the presence of fat tissue between muscle bundles and its extension into the myocardium at a distance from the subepicardial fat. The excess of fat is often noted first in the perivascular areas.

Fat may also infiltrate the atria, more commonly the right atrium than the left. It is possible that some forms of cardiac arrhythmia or electrocardiographic changes may be induced by infiltration of fat with compression of the sinus node.

The clinical signs and symptoms of fatty infiltration should be those of right heart failure. Yet fatty infiltration of the myocardium is practically never diagnosed during life. It stands to reason that a right ventricle partially replaced by fat would have diminished reserve power. While it may cause death

rarely, it often serves to explain death of a patient who has relatively little bronchopneumonia or small pulmonary emboli. In these instances it is the right ventricle which is called upon to do extra work. A right ventricle with much of its myocardium replaced by fat may not be able to compensate for the slightly increased demand upon it and such a patient may die, sometimes unexpectedly, in the absence of premonitory symptoms.

The occurrence of rupture of a heart from severe fatty infiltration is questionable. A number of such instances are described in the older literature, and in 1939 an example was reported by Donat. If rupture occurs at all, it is extremely rare.

Fatty infiltration is often found in the markedly obese and may also be present in the heavy beer drinker. The so-called "beer-drinker's heart" of the old literature referred to fatty infiltration. However, fatty infiltration of the heart also occurs in the absence of obesity. Other terms used for this entity are fatty heart and lipomatosis of the heart (lipomatosis cordis).

Fatty Degeneration of Myocardium. This condition may result from quantitative or qualitative alterations of the blood, especially in pernicious anemia or leukemia. It is common in acute infections, especially diphtheria, scarlet fever, sepsis or other infectious diseases accompanied by toxin production and high fever. It follows intoxication with phosphorus, arsenic, chloroform, iodoform, ether, alcohol, and eating of poisonous mushrooms. Partial or complete obstruction of the coronary arteries and long-standing pericardial exudate are said to cause it.

In experimentally induced ischemia in dogs, fatty changes occur in the myocardial fibers as early as 1 hour after injury. These gradually increase in intensity and persist for as long as 14 days (Wartman *et al.*, 1956). The anoxia of high altitudes may also cause fatty degeneration of the myocardium, especially if hypertrophy is present (Linzbach, 1952). Kaufmann (1929) reported that fatty degeneration of the myocardium was present in 50 per cent of his cases of cardiac hypertrophy resulting from valvular defects, kidney disease, emphysema or kyphoscoliosis. He

mentioned that when valvular defects are present there is often marked fatty degeneration of the papillary muscles, particularly in the left ventricle. Fatty change also occurs after intoxication with alcohol and carbon monoxide and in diabetes mellitus and acute liver necrosis. In rabbits, fat has been observed to accumulate in the myocardium following decerebration or cauterization of the brain (Valdes, 1954).

Concerning the source of the fat in the myocardial fibers, the work of Dible (1934), Dible and Gerrard (1938) and Wartman and associates (1956) has established that most of the fat that appears in the myocardium in fatty degeneration is exogenous, being brought to the heart from the body depots. Ordinarily the heart burns much fatty acid but when the myocardial cells are injured, the fatty acids are not completely utilized and fat accumulates in the cell.

The term, fatty degeneration of the myocardium, denotes excessive accumulation of fat and fatty substances in the myocardial fibers. The fat occurs in the form of droplets, most commonly in the cytoplasm but also in



Figure VII-6. Fatty degeneration of myocardium of papillary bundles of left ventricle. (WCGH, 49 A 50.)



Figure VII-7. Frozen section of myocardium stained with Sudan IV to show focal deposition of fat droplets within the fibers. X 180

the nuclei. Dible (1934) recognized two forms of fatty degeneration. One form is patchy in distribution, having the well-known thrush-breast gross appearance (Figures VII-6 and 7), while the other is diffuse and causes the myocardium to look greasy. Although it is not known whether they are entirely distinct lesions or may progress from one to the other, nevertheless it seems desirable to retain the distinction until more is known of the nature of this disorder.

Percentage of fat in normal myocardium. According to Dible (1934), the amount of fat in the normal myocardium, after removal of the subepicardial fat and the fat adjacent to the coronary arteries, is 1.74 per cent with a range of 1.4 to 2.1 per cent, and the corresponding iodine value is 123 with a range of 118 to 130.

These values were obtained from the hearts of presumably normal persons who died either accidentally or from diseases which produced no detectable pathologic change in the heart. The amount of fat was determined by the method of Leathes and Raper and the iodine values by Dan's method. There was no difference between

the fatty content of the subepicardial half and that of the subendocardial half of the left ventricle. Dible reported that the percentage of fat in children's hearts is lower than that of adults, but gives no data in support of this statement. He asserted that the fat content of the cardiac muscle reflects to some extent the general state of nutrition of the body, but that the range of variation in the amount of fat is not wide, if the extremes of inanition and obesity are excluded.

Patchy type of fatty degeneration of myocardium. In this form of fatty degeneration the changes are fairly sharply limited to the subendocardial portion of the myocardium, particularly the interventricular septum of the left ventricle, the papillary muscles and, occasionally, to corresponding locations in the right ventricle (Dible, 1934). Localization in the subendocardial portion of the myocardium and the papillary muscles of the left ventricle suggests that patchy fatty degeneration may occur more frequently in some muscle bundles than in others, for this is the distribution of the superficial sino-spiral and bulbospiral muscles of the left ventricle. Such an explanation would also account for the infrequent involvement of the right ventricle, for these muscles do not make up the papillary muscles or subendocardial layer of that chamber (Lowe and Wartman, 1944). The characteristic gross appearance is seen in the ventricular septum and consists of a peculiar yellow mottling which has been likened to the breast of a thrush or to the coat of the tiger or tabby cat. The changes are most marked in the inner portion of the ventricular muscle beneath the endocardium, although minor amounts of fat can occasionally be detected in other parts of the heart.

Microscopically the patchy character of the lesion is also apparent, the areas of fatty degeneration being separated by myocardium which shows either minimal changes or none at all. The fat is found within the cytoplasm of the myocardial fibers in the form of globules which may be so large as to disrupt the fibers.

Dible found that, while the amount of fat in the myocardium in apparently normal

areas was 2.3 per cent, in visibly degenerated areas it was 3.5 per cent, an increase of 52 per cent over the amount of fat in normal heart muscle. The mean iodine values for these areas were 110.3 and 92.5, respectively.

Diffuse type of fatty degeneration of myocardium. The myocardium is pale and greasy, soft, flabby and friable. Both the right and left ventricles are involved about equally. Microscopically the fat globules are small and so diffusely distributed that every fiber is peppered with them. The entire thickness of the interventricular septum is affected and there is no difference between the amount of fat in the inner and outer portions.

On chemical analysis, the left ventricle contained an average of 3.3 per cent of fat, an 80 per cent increase over the mean value for the normal left ventricle; the iodine value was 104 (Dible, 1934). Kaufmann (1929) stated that Krehl found 26 per cent of fat in the cardiac muscle of a person with phosphorus poisoning (ether extraction of dried myocardium), whereas by the same method normal myocardium contained 11 per cent of fat. Chemical methods indicate that the heart contains no protein-bound fat although histochemical methods suggest that some of the fat may be bound to protein.

There is no agreement among clinicians concerning the clinical manifestations of fatty degeneration of the myocardium. Cases have been described in which the patient's death was attributed to a severe degree of fatty degeneration (Carvin, 1940). On the other hand, in some advanced cases of fatty degeneration death cannot be attributed to it.

Fatty degeneration of myocardium in newborn. Rarely a newborn child, usually a robust infant, will develop cyanosis, hemoglobinuria, icterus and shock on the first day of life and autopsy will reveal severe fatty degeneration of the heart and liver, with multiple punctate hemorrhages in all organs. This condition has been given the name of *Winkel's disease* in the German literature and, if the cyanosis is particularly marked, it is called *Buhl's disease*. Both are usually associated with a progressive, septic infection. In *Buhl's disease* the umbilicus and intestines are usu-

ally infected, but in *Winkel's disease* they are spared and there is commonly an infection with *Bacillus (Escherichia) coli* (Kaufmann, 1929).

Fatty Degeneration of Endocardium. Fatty degeneration of the valvular endocardium occurs in the form of white and yellow-white plaques on the atrial aspect of the mitral and tricuspid valves, usually at or near the base, and is often associated with calcification. Microscopically numerous cells are filled with fine fat droplets which lie between the connective tissue cells. Calcium may be present and in some cases, small mononuclear cells. These lesions are common in old people, but may be seen in children or young adults who have died from anemia, intoxication or infection. They are thought to result from the mechanical effects produced by closure of the valve during systole (Kaufmann, 1929).

The Heart in Lipidoses. The heart may be involved in the lipid-storage diseases, focal accumulations of foamy cells being deposited in the endocardium or the arteries. Lesions may be found beneath the endocardium of the ventricles or atria and in the myocardium, and consist of nodular aggregations of foam cells and a reactive low-grade inflammation. The foam cells may contain lipids of different sorts, depending upon the disease process, or may contain no lipid. In the coronary arteries the patches may cause occlusion with resulting myocardial infarction and death. There are no special features of the lesions of the heart in this disease.

Disturbances of Carbohydrate Metabolism

Normal Metabolism of Mammalian Heart. It has long been suspected that glycogen disease is basically a defect in carbohydrate metabolism, and considerable evidence has now been obtained to substantiate this view. Ordinarily the heart functions almost entirely on aerobic metabolism, utilizing carbohydrate (glucose, pyruvate and lactate), fatty acids and amino acids for its energy requirements (Bing, 1954). All these substances are brought to the heart by the coronary blood and are metabolized through the various steps

of the Krebs cycle, with liberation of large quantities of energy needed for cardiac contraction (Jennings and Wartman, 1957). All mammalian hearts also maintain an intracellular supply of glycogen, which can be metabolized anaerobically, as a reserve source of energy. The amount, however, varies in different species (Merriek and Meyer, 1954). In general, animals such as mice, which have rapid heart beats and are dependent on aerobic metabolism, have small quantities of intracellular glycogen in reserve, whereas animals with relatively slow heart rates usually have larger stores of glycogen. In human beings the exact extent to which glycogen participates in normal metabolism is unknown, but under abnormal conditions, such as anoxia, glycogen is obviously a source of energy (Yokoyama *et al.*, 1955).

Chemical studies have shown that myocardial glycogen exists in two forms, one extractable with cold trichloroacetic acid (TCA) and the other a residual glycogen released from tissue only after digestion with hot potassium hydroxide. Experimental evidence strongly suggests that these two forms react differently to changing conditions. For example, Merriek and Meyer (1954) have shown that in anoxia TCA-reducible glycogen is decreased to an even greater degree than the total amount of cardiac glycogen. The residual glycogen is believed to be bound to protein and to be more readily available to metabolic mechanisms leading to glycolysis.

It has also been shown that the carbohydrate metabolism of an individual is profoundly affected by his (1) enzymatic constitution, (2) hormonal balance, and (3) electrolyte pattern in the intracellular and extracellular fluid. Disturbances in any of these three factors may cause disease; for example, there may be deficiency of an enzyme, as in glycogen-storage disease; deficiency of a hormone, as in diabetes or hypoglycemia; or disturbance in relationship of electrolytes, as in acidosis (Najjar, 1952). The synthesis and breakdown of glycogen depends on certain specific enzymatic systems that are arranged more or less in an assembly line. When a key enzyme is absent, such as glucose 6-phosphatase which furnishes glucose to the blood stream, the patient becomes hypoglycemic and glycogen accumulates as in classical glycogen-storage disease. Or glycogen may fail to break down because it is ab-

normal, as in some cases of glycogen disease of the heart.

The amount of histochemically demonstrable glycogen in the hearts of normal infants has been found to vary widely, often approaching or at times exceeding the amounts found in glycogen-storage disease of the heart. This, of course, complicates the diagnosis of this disease and the mere demonstration of abundant glycogen in the myocardium of an enlarged heart is not sufficient evidence for making such a diagnosis. In most normal adult persons only slight to moderate amounts of glycogen can be detected with Best's carmine stain, the Bauer reaction or the periodic acid-Schiff technique applied to tissues digested with diastase (Mowry and Bangle, 1951). Occasionally, however, large amounts are observed.

General Features of Glycogen-Storage Diseases. Our concept of glycogen-storage diseases has been much altered by the work of Andersen (1952) and Cori (1952) which indicates that there is more than one form of the disease.

1. *Classical von Gierke's disease of liver*, associated with hypoglycemia, acidosis, and enlargement of the liver. The metabolic defect lies in failure of the liver to form glucose from glycogen, owing to absence or reduction of the enzyme glucose-6-phosphatase which is responsible for furnishing glucose to the blood stream from the phosphorylated sugar, glucose-6-phosphate. When this coenzyme is absent, glycogen cannot be converted to blood glucose. However, the synthesis of glycogen from sugar continues, with resulting accumulation of glycogen. The reduction in this enzyme also explains why liver glycogen does not disappear postmortem. The glycogen shows no abnormalities and is also deposited in liver and kidneys.

2. *Glycogen disease of liver with cirrhosis and death from hepatic failure.* Here a metabolic defect results in formation of glycogen of abnormal molecular structure; the glycogen accumulates in the liver, spleen and reticulo-endothelial system which react to it by excessive production of fibrous tissue.

3. *Galactosemia* resulting from inability of the body to utilize the galactose derived from milk lactose.

4. *Glycogen disease of heart.*

Glycogen Disease of Heart. Glycogen is deposited mainly in cardiac and skeletal muscle, with increased amounts being present in most parenchymal cells. The nature of the metabolic defect in this form of glycogen storage disease is not known but the defect cannot be caused by a lack of glucose-6-phosphatase since muscle does not normally contain this enzyme. However, it is possible that a specific enzymatic lesion will be found, possibly a deficiency of amylo-1, 6-glucosidase (Illingworth *et al.*, 1956).

All forms of glycogen-storage disease are familial and probably inherited as recessive genetic traits. In severe involvement, the heart is distorted and round in shape, so that both ventricles contribute to the formation of the apex. The heart may be enormously enlarged. The thickness of the myocardium of the left ventricle may measure 29 mm. and that of the right ventricle, 9 mm. Cases have been reported in which the heart weighed as much as 260 grams in children less than 4 years of age. The muscle has a rather glassy homogeneous appearance but is not usually as gray as in amyloid disease. The columnae carneae are considerably flattened because of the hypertrophy and dilatation. The valves and coronary arteries are not involved.

Microscopically the appearance is quite characteristic. The myocardial fibers are large, measuring as much as 50 micra in diameter, and there is extensive vacuolization of the sarcoplasm, the vacuoles giving a positive reaction with Best's carmine stain, and with the iodine stain for glycogen. Both stains are apparently reliable and give similar results, as does the periodic acid-Schiff reaction. The heart fibers may be changed almost beyond recognition and, when cut tangentially, may appear as hollow cylinders surrounded by a delicate, striated, protoplasmic wall. The nuclei are compressed and displaced to the periphery. Often the most marked deposits of glycogen are just beneath the endocardium (Haymond and Giordano, 1946).

Several cases have been reported in which a slight degree of aortic stenosis was associated with the glycogen infiltration of the heart.

Age incidence. Nearly all the cases which have been reported concern children between the ages of 4 months and 1 year, and usually death has been sudden. In a few cases the children lived to the age of 4 years.

Chemical analysis of organs. Chemical analysis of the tissues from cases of glycogen disease of the heart are reported by van Creveld (1939). He gives the percentages of glycogen in the various organs as follows: heart, 7.97, liver, 9.13, spleen, 1.46, adrenal, 1.25; skeletal muscle, 9.39, lung, 0.03; spinal bone marrow, 0.583; while the concentration in the blood after death was 18 mg. per 100 ml. The percentages in a control case with marked hypertrophy of both ventricles caused by a patent interventricular septum were as follows: left ventricle, 0.055, right ventricle, 0.07; liver, 0.103; kidneys, 0.062, spleen, 0.01, muscle, 0.011; the concentration in the blood during life was 12.75 mg. per 100 ml. The glycogen is usually deposited in the following locations: the fibers of the heart muscle, liver cord cells, especially at the periphery of the lobules, the primitive bundles of the skeletal muscles; the convoluted tubules of the second order and collecting ducts of the kidney; the splenic pulp, especially at the borders of the follicles; the zona reticularis of the cortex of the adrenal gland; spinal bone marrow; cell bodies of ganglion cells; hair follicles of the skin; walls of blood vessels; and the connective tissue cells in most organs.

A peculiarity of this disease is that the glycogen apparently does not break down, and hence is found in the organs for a long time after autopsy and even after the organs have been fixed in aqueous solutions. This is in marked contrast to the behavior of glycogen in most other diseases and in normal organs from which it disappears promptly after death unless special measures are taken to preserve it. In glycogen disease the glycogen is usually well preserved for as long as several months and can be easily stained with routine glycogen stains after this length of time, even though the fixing fluid has been repeatedly changed. Finkelstein (1936) was able to demonstrate the presence of glycogen in the heart 13 years after it was placed in fixative. The glycogen may also be preserved by refrigerating fresh organs.

Circumscribed Glycogen Disease. Besides



Figure VII-8. Nodular glycogenic infiltration of myocardium. Note large circumscribed white nodule. (WCCG, 40 P 50.) (From Haymond and Giordano, *Am. J. Clin Path.*, 16:651, 1946. Courtesy of authors and The Williams & Williams Co.)

the diffuse form which has been described above, the glycogen may be deposited focally. This form is sometimes called circumscribed glycogen disease of the heart or *cardiomegalia glycogenica circumscripta* (Finkelstein, 1936). In these cases there is usually, in addition to the glycogen infiltration, an increase of connective tissue with necrosis and fatty degeneration of the myocardial fibers. The glycogen is usually distributed subendocardially but not exclusively so.

Congenital Nodular Glycogenic Infiltration of the Myocardium was formerly called *rhabdomyoma*.

An example of this lesion is given in the excellent and detailed description by Farber (1931) who reported its occurrence in a 6-month-old female infant in association with tuberous sclerosis of the brain. The heart was enlarged, weighing 90 grams. A number of masses were found bulging into the right atrium and right ventricle which varied in size up to about 1 cm. in diameter. One mass obstructed the orifice of the tricuspid valve. A number of small nodular excrescences were also present between the papillary muscles near the apex of the right ventricle. The left atrium was

not involved but a few small nodules, each approximately 1 mm. in diameter, were scattered in the myocardium of the left ventricle. On section the nodules were yellow or gray-yellow and moderately firm, and the cut surfaces smooth and slightly bulging.

Location of nodules. The nodules may be present in both atria (Olsen and Cooper, 1941) or in the ventricles (Figure VII-8) and atria (Mitani, 1934) or in the ventricles alone (Steinbiss, 1923). They may be found close to the bundle of His.

Microscopic features. The following microscopic description is taken from Farber (1931). Examination of tissue fixed with Zenker's solution disclosed large vacuolated spaces of round or oval shape and irregular size, giving the sections a loose, spongy appearance (Figures VII-9 and VII-10). Numerous heavy connective tissue trabeculae, containing blood vessels, coursed through the lesion, giving off finer and more delicate branches which ramified among the large vacuolated spaces. Thick protoplasmic walls surrounded the spaces, and between them in

places was a thin, delicate connective tissue reticulum. Some of the spaces were empty, while within other spaces were cells with many processes. The cells varied greatly in size and shape, depending in part on the size of the spaces in which the cells were located. The processes ran from the central protoplasmic mass in bizarre and irregular fashion. Sometimes they anastomosed richly and divided into finer elements until they merged with the wall. Often the processes were short, plump, and few in number, in places failing to merge with the wall. On close examination, these processes were transversely striated by rows of delicate granules. With suitable stains, these granules stood out clearly and the processes as well as the wall of the spaces showed numerous definite cross-striations.

The cells generally had but 1 nucleus, occasionally 2, and rarely 3 or 4 nuclei. Sometimes clear spaces surrounded the nuclei and, in such cases, the processes were generally

short and plump. Each nucleus usually contained a single nucleolus. Occasional evidence of direct division was noted and no mitotic figures were seen. Sections stained with Best's method showed large amounts of glycogen in the form of fine droplets filling the spaces and gathered thickly along the cell processes. The vacuolated spaces and the cells within them are apparently most characteristic and their presence is emphasized in most reports. These cells are often called "spider cells" (Figure VII-11). The vacuolated spaces are filled with glycogen. The tissue between the spaces is sometimes composed of large polygonal branching cells having finely granular and eosinophilic cytoplasm (Labate, 1939). Steinbiss (1923) stated that some of these lesions, after degeneration, may go on to scar formation.

Frequency. Farber (1931), in addition to his case, found reports of only 33 undoubted cases of the multiple type and 8 of the single type. Labate (1939) added 8 new cases which he



Figure VII-9. Nodular glycogenic infiltration. Note the large empty spaces which had contained glycogen. Same case as Figure VII-8. Hematoxylin and eosin. X 100. (WCGH, 45 P 191B.)

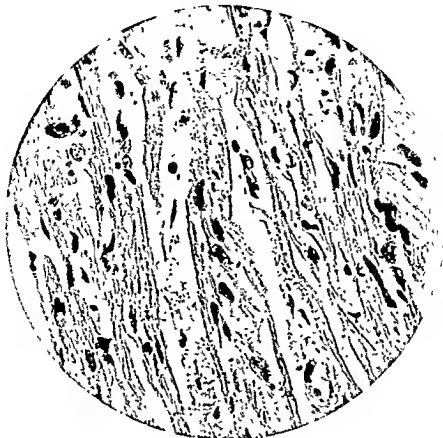


Figure VII-10. Nodular glycogenic infiltration Same case as Figure VII-8.
X 400.

collected from the literature and 1 which he had observed. Olsen and Cooper (1941) recorded an instance with multiple nodules in the heart. Batchelor and Maun (1945) collected reports of 62 cases, 10 of which had appeared in the American literature, and added another example. Kidder (1950) found a total of 69 such tumors. In regard to the apparent rarity of these lesions, Steinbiss stated that rhabdomyomas are often associated with tuberous sclerosis. These patients do not necessarily die in infancy but, because of concomitant mental disturbances, are later admitted to institutions for the care of the feeble-minded. He pointed out that autopsies in mental institutions are often not performed or may be limited to an examination of the brain, and stated that, if more complete autopsies were performed, more rhabdomyomas would be found. Steinbiss found 6 rhabdomyomas among 31 patients with tuberous sclerosis who died in mental institutions. Kirch (1927) also asserted that rhabdomyomas are not as rare as generally believed.

Age and race. In the cases of rhabdomyoma of the heart reviewed by Farber, 12 of the patients were more than 3 years old, the oldest being 35.

Of the 63 cases reviewed by Batchelor and Maun (1945), 42 were less than 3 years old.

Hueper (1935) was the first to report this lesion in the Negro. Pratt-Thomas in 1947 recorded another such lesion in a premature Negro infant.

Clinical features. Kirch (1927) noted that the lesion had never been diagnosed clinically. In a number of instances, symptoms referable to associated tuberous sclerosis of the brain could be elicited (Steinbiss, 1923). Wegman and Egbert (1935) reported a patient in whom cardiac arrhythmia was detected clinically. In the reports reviewed by Batchelor and Maun, cyanosis was listed as a frequent symptom, especially in newborn infants and in those who died unexpectedly. Monekeberg (1924) mentioned that in several patients evidence was noted of stenosis of the orifice of the pulmonic valve, produced by tumor nodules within the conus pulmonalis. In practically all of the reported instances, however, the finding of nodular glycogenic infiltration was unexpected.

Association with tuberous sclerosis and other lesions. Labate (1939) stated that in 57 per cent

of the 29 patients in the cases reviewed by him, tuberous sclerosis of the brain was also found. In Batchelor and Maun's (1945) series, the incidence of tuberous sclerosis was 50 per cent. They asserted that the frequency of association of the two lesions is actually much higher. Various tumors of the gloma group have also been found associated with tuberous sclerosis. Kidney tumors, angiomyosarcomas, angioliipomas, cysts, nests of embryonal tissues, various malformations, and adenomas, especially sebaceous adenomas, are also frequently encountered in patients with congenital rhabdomyomas of the heart.

Occurrence in animals. Similar lesions in the heart have been observed in animals. Hieronymi and Kukla (1921) described a number of smaller and larger nodules in the heart of a four-month-old pig. Also Joest (1923) and Clausen (1938) each found a solitary rhabdomyoma in the heart of a pig. Pires and Mucciolo (1939) reported such a tumor in a cow, and Hueper (1941) described multiple rhabdomyomatous nodules in the heart of a guinea pig, the heart weighing 245 grams.

Wollbach (1907), by the use of the phosphotungstic acid and hematoxylin stain, offered conclusive evidence that the spaces were located within the muscle fibers. Seiffert (1901), in a report before the German Pathologic Society, first suggested that the empty spaces within the muscle fibers might represent dissolved glycogen. In the discussion of Seiffert's communication, Marchand supported this opinion and Askanazy, stated that he had actually found glycogen in a rhabdomyoma which had come under his observation. Rehder (1914) clearly demonstrated the presence of glycogen in "tumor" cells, and in most of the lesions recorded later, glycogen was demonstrable. Ribbert (1915) emphasized a local disturbance somewhere during the growth of the heart muscle. He thought that muscle elements in an early stage of development were thus separated from the rest of the myocardium and grew independently. He, therefore, classified rhabdomyomas as choristomas. Rehder, however, regarded rhabdomyomas as simple malformations of muscle structures and grouped them among hamartomas. Both authors emphasized that because of the multiplicity of the lesions, their appearance, and their lack of tendency to grow, they should not be classified as tumors.

Steinbiss (1923) thought that both rhabdomyomas and tuberous sclerosis might be explained on the assumption of an "excess" in the cardiac and brain Anlagen. Both Monckeberg (1924)

and Kirch (1927), concluded that rhabdomyomas should not be regarded as true tumors. Hamilton-Paterson and Castleden (1942) classified this lesion among benign congenital tumors arising from developing myocardial elements (congenital rhabdomyoma, dysontogenetic rhabdomyoma, hamartoma). Hertzog (1949), who described diffuse rhabdomyomatosis of the heart in a 2-month-old infant, also interpreted this tumor as a hamartoma.

The modern concept of rhabdomyoma can be traced to von Gierke's first publication of his "hepatonephromegalia glycogenica" in 1929. In it he also mentioned an instance in a child which was the result of glycogen infiltration. Putschar (1932), 3 years later, published the first detailed report of congenital glycogen infiltration of the heart in a 4-month-old child. It is interesting that just 10 years earlier, Schminke (1922) had recorded an instance of congenital hypertrophy of the heart, the result of "diffuse rhabdomyomas" with much glycogen obvious within the muscle fibers. Pompe (1933) referred to this case as being typical of von Gierke's glycogen-storage disease. Pompe also ventured the opinion that a number of other instances reported as idiopathic hypertrophy of the heart probably are examples of von Gierke's disease. Curiously enough, as early as 1864, Virchow



Figure VII-11. So-called rhabdomyoma. Note "spider cell." Pollak's modification of trichrome stain. X 500, original magnification, X 365. (From Pratt-Thomas, *Am. J. Path.*, 23:189-199, 1947. Courtesy of American Journal of Pathology.)

thought that perhaps idiopathic hypertrophy of the heart could be explained by a diffuse rhabdomyoma of the heart.

Humphreys and Kato (1934) suggested that, in view of Pompe's observations it might be well to examine critically the rare cardiac rhabdomyomas to see if they represent localized or diffuse glycogen disease (cardiomegalic glycogen-storage disease). Olsen and Cooper (1941) stated that, because of poor terminology, nodular glycogen tumors have been confused with rhabdomyomas, which they classified as true neoplasms. For this reason they recommended use of the term, *congenital nodular glycogenic degeneration of the myocardium*. This term conforms with the objective findings of the disease without suggesting a neoplastic origin or implying an exact knowledge of the etiology. While these authors classified all congenital "tumors" of this type as localized lesions of glycogen-storage disease, they did not deny that true rhabdomyomas exist in the heart, perhaps without the presence of much glycogen within the fibers. Batchelor and Maun (1945), apparently in partial agreement with Olsen and Cooper (1941), suggested the term "congenital nodular glycogenic tumors of the heart" for their case report. Leach (1947), in the summary of his report, spoke of rhabdomyoma or congenital nodular glycogenic tumor. Sussman and Stasney (1950) believed that congenital nodular tumors of the heart should not be classified as neoplasms, but as hamartomas or tumor-like malformations consisting of misplaced striated muscle tissue. They reported the occurrence of a lesion in a patient who had an arrhythmia. Prichard (1951) regarded rhabdomyomas of the heart as hamartomatous nodules which may regress. He believed that they represent focal arrest in maturation of the cardiac muscle. However, he did not believe that the existence of diffuse true rhabdomyomas has been proved, and stated that reported examples are probably manifestations of localized glycogen storage disease.

Histochemical property. Hueper (1941) pointed out that the glycogen contained in the primitive muscle cells of rhabdomyomas is much more soluble in the ordinary fixatives than the glycogen stored in the various organ cells, such as liver and heart, in glycogen-storage disease. This difference is brought out strikingly by the fact that glycogen in nodular glycogenic infiltration has been demonstrated only rarely, the glycogen being removed from these cells by fixation in aqueous media before the proper staining procedures are applied; while the glycogen present in the

tissues of von Gierke's disease has been demonstrated by chemical and staining methods after having been in fixing fluids for weeks or months. In the latter instance, the glycogen is not only markedly resistant to postmortem hydrolysis but is also much less soluble in watery agents than is ordinary glycogen. This histochemical property, in conjunction with the demonstration of "spider cells" and various myofibrillar evolutionary manifestations in the primitive myocardial cells, may help in distinguishing between nodular glycogenic infiltration and myocardial tissue changes associated with von Gierke's glycogen-storage disease.

Summary. The myocardium may be the seat of either a localized or widespread lesion which in the earlier literature was classified as congenital rhabdomyoma. It was soon recognized that this lesion is not encapsulated, that it merges imperceptibly with the surrounding healthy myocardium, that morphologic evidence of malignancy is never encountered, and that metastatic growths are not found. It seems to grow only at the same rate as the adjacent normal muscle structure. Because of its histologic features and because of associated lesions, especially tuberous sclerosis of the brain, the cardiac nodules were early regarded as muscle malformations and were classified as hamartomas. The rich glycogen content of the fibers of rhabdomyomas has often been emphasized, and when glycogen-storage disease became known, it was soon suggested that these congenital rhabdomyomas were expressions of this disease and terms like "nodular glycogenic degeneration of the heart" and "glycogenic tumors of the heart" were coined. At present the etiology of congenital rhabdomyomas is still unsettled but it is generally agreed that they are not true tumors. Are they hamartomas or do they represent localized manifestations of glycogen-storage disease (von Gierke's disease)? The differences in the chemical behavior of the glycogen in von Gierke's disease from that in the nodules, as Hueper has emphasized, are not sufficiently distinctive to be used as means of distinguishing the two lesions.

Cardiac Glycogen in Other Diseases. Frequently in diabetes mellitus the myocardium contains large amounts of glycogen which,

however, is not clearly related to the severity, duration or control of the disease or to the nature of the treatment (Warren, 1930, Mowry and Bangle, 1951). An increase in myocardial glycogen has also been described in children dying from pneumonia and dysentery and in adults dying from the effects of hypertension or from pneumonia (Provotorova, 1951).

In myocardial infarcts produced experimentally in dogs, glycogen depletion begins within one hour and is complete within a few hours. During the stage of healing, increased quantities of glycogen are observed in the surrounding myocardial fibers (Yokoyama *et al.*, 1955). In rats anoxia, maintained for 150 minutes, causes a reduction in concentration of glycogen from 500 mg. to about 170 mg. per 100 grams of tissue. According to Cordier and Dessaux (1952), the reduction is chiefly in the fraction soluble in cold trichloroacetic acid (to 22 per cent of normal) and less (to 37 per cent of normal) in residual glycogen. A slight decrease was observed in shock, but none after thermal or histamine injury (Cordier and Dessaux, 1951).

Disturbances of Calcium Metabolism

Calcification of the heart may be either dystrophic or metastatic, the former being much more common.

Dystrophic Calcification may occur in any area of dead tissue that is not infected and that is so large or so situated that it cannot be absorbed. Hemorrhagic extravasates are particularly susceptible to calcification as are hyalinized scars. Calcification of hyaline scars may occur whether necrosis is present or absent; it has been related to low production of carbon dioxide in a slowly metabolizing tissue, with consequent development of a local zone of relative alkalinity and reduced calcium solubility. Dystrophic calcification may also take place without change of the physiologic levels of any of the chemical constituents of the blood (Gore and Arons, 1949).

Dystrophic calcification of the pericardium (Figure VII-12) may occur in rheumatic fever and tuberculosis and cause constrictive pericarditis. Calcium is deposited less frequently in pericarditis caused by other bacteria, among which may be mentioned pneumo-

cocci, streptococci and staphylococci. It may also be found in hemopericardium. Occasionally fibrous pericardial plaques ("soldier spots") may be calcified.

The valves of the heart are, of course, frequently the site of dystrophic calcification. Invariably there is previous valvular disease which is almost always rheumatic in origin (Karsner and Koletsky, 1947). Calcification of vegetations occurs frequently. Calcium may also be deposited at the base of the valves, particularly in the ring of the mitral valve, where it forms an annular structure usually on the ventricular aspect of the valve. These lesions are discussed elsewhere.

Deposition of calcium in the myocardial fibers is often regarded as a late effect following necrosis. Yokoyama and associates (1956), however, have observed deposition of calcium at the margins of experimental infarcts as early as 1 hour after the onset of ischemia. It seems likely on the basis of the results of these and other experiments (Gallagher *et al.*, 1956) that the primary lesion may have been a change in the semipermeable properties of the cell membrane with entry of calcium ions. Since calcium ions inhibit oxidative phosphorylation (Potter, 1947; Lehninger, 1949), entry of calcium into the cell would stop production of energy.

Metastatic Calcification, in contrast, is associated with increased availability of cal-

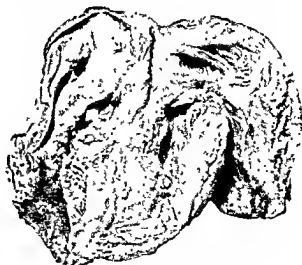


Figure VII-12. Calcification of pericardium following pericarditis of unknown etiology. Patient was a 51-year-old woman, an inmate of the psychiatric hospital. (WCGH, 35 A 285.)

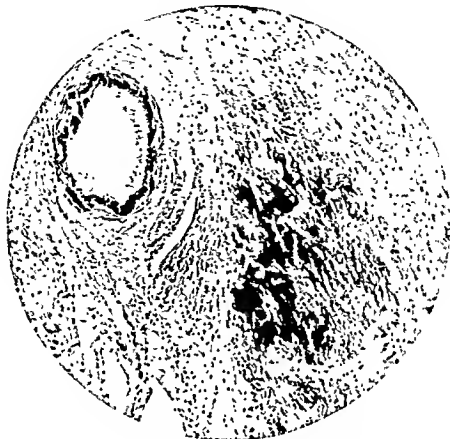


Figure VII-13. Calcification of pericardium resulting from excessive ingestion of Vitamin D. Case of Dr. W. A. Stryker X 150. (WCGH, 45 P 101 E.)

cium and is usually accompanied by deposits of calcium in other organs, particularly the lungs, stomach, kidneys, spleen and liver. It is found in association with destructive bone lesions, hyperparathyroidism, hypervitaminosis D, and renal insufficiency. In metastatic calcification, the deposits have a characteristic distribution, being much more likely to accumulate in tissues which have a hyaline structure. For example, the hyaline structure of elastic tissue serves to explain the involvement of arterial and endocardial (right atrial) elastica in metastatic calcification. The selective localization of metastatic deposits of calcium is to be explained not only by the increased availability of calcium, but also by the structure and physiologic activity of the involved tissues. Dystrophic calcification, on the other hand, owes its occurrence purely to local pathologic changes and has no characteristic distribution (Wells, 1925; Mulligan, 1947; Core and Arons, 1949).

The annulus fibrosus of the mitral valve is commonly calcified. In a series of 230 autopsies on patients in the age group 60-99 years, Geill (1950) found the lesion to be common in old age, more frequent in women than men, and not related to preceding endocarditis. The deposits of calcium varied from a few millimeters in diameter to complete involvement of the ring, but did not produce stenosis or insufficiency. The lesion sometimes gave rise to late diastolic murmurs, and calcium offshoots sometimes caused disturbances of conduction.

Core and Arons (1949) found that calcium deposits in the myocardium were laid down on necrotic muscle fibers. Ordinarily the necrotic material is absorbed before calcium is deposited. Thus, myocardial calcification is usually dystrophic. However, it may be metastatic, as for example in cases of vitamin D intoxication (Figure VII-13). Also, it is to be noted that under circumstances which favor metastatic calcification,

there may be an augmented and accelerated tendency towards the development of dystrophic calcification. The process in the heart muscle in these cases is therefore regarded as an example of accelerated dystrophic mineralization. Renal failure and azotemia are usually present.

Gore and Arons believe that the laws of mass action and of ionic equilibrium of saturated solutions of poorly soluble salts explain, in the case of tricalcium phosphate, the ease with which precipitation may be induced by increases of either calcium or phosphate. According to these authors, the pathogenesis of the basic myocardial lesion is varied, resulting from ischemia, infection or unknown causes. They also point out the possible influence of uremia in causing multiple tiny foci of myocardial necrosis which subsequently calcify. Special staining reactions for iron and calcium showed the fallacy of making a diagnosis of calcification from a preparation stained with hematoxylin and eosin. In three of their 13 cases the deposit proved to be iron only. In six others the calcium was associated, but not always co-extensive, with iron.

When the calcification of the myocardium is massive, it may be detected in roentgenograms during life (Cutler and Sosman, 1924; Bishop and Roesler, 1934). Occasionally it is possible to diagnose cardiac aneurysm because the scar of the infarct is calcified (Parkinson *et al.*, 1938). Calcified nodules situated in the bundle of His

may cause complete heart block (Yater and Cornell, 1935). About 10 per cent of old infarcts show calcification.

Calcification of coronary arteries is common and is discussed in Chapter VIII.

Pathologic Ossification. Heteroplastic deposits of bone have been described in the heart valves and in the myocardium of all chambers including the conduction system. Usually they are preceded by extensive calcification.

Finestone and Geschickter (1949) are of the opinion that if in addition to certain chemical criteria there is a diminished blood supply, calcium will be deposited in the tissues. If at a later date the blood supply is sufficiently improved by increased vascularity, such as may result from an inflammatory response to the presence of the calcium, then ossification may occur. In support of this theory they point out that the osteoblast is no longer regarded as a specific cell endowed with the power of producing bone, but that any connective tissue after preliminary dedifferentiation to primitive mesenchyme may be built up again in the form of any other connective tissue. Thus they believe that the only factors necessary for bone formation in mesenchymal tissue are an excess of calcium and an adequate blood supply. The presence of marrow cells has been explained in a similar fashion.

THE HEART IN NUTRITIONAL DISEASES

Undernutrition and Starvation

Keys (1948) has summarized the cardiovascular effects of undernutrition and starvation. Both acute and prolonged undernutrition produce a reduction in the size of the heart comparable to the loss of weight of the body as a whole. Though reduction in epicardial fat is conspicuous, the major portion of the loss of weight is the result of reduction of the muscle in all chambers. Microscopically, there is first a reduction in the size of the muscle fibers. Later there is evidence of degeneration: cloudy swelling, loss of striation, vacuolization, and occasionally fatty degeneration. The heart may also show brown atrophy.

The principal functional effect of under-

nutrition and starvation is reduction of cardiac output. Bradycardia may be pronounced, and there is reduction of systolic blood pressure, peripheral circulation, and venous pressure. While the presence of low venous pressure would seem to indicate that the cardiac state is not an important factor in the appearance of edema in starvation, it may be that physical exertion increases the venous return beyond the capacity of the atrophic heart. If this is the case, then famine-edema may be essentially the same as the edema of congestive heart failure from other causes, though the possible contribution of hypoproteinemia which accompanies undernutrition should not be overlooked. It has been noted that starved persons may first develop cardiac failure following resumption of feeding.

The atrophy described above may be seen in the undernutrition of persons otherwise healthy who are deprived of adequate food or who restrict their intake, as in anorexia nervosa. It occurs also in the course of chronic debilitating diseases, such as cancer or tuberculosis, and such endocrine disturbances as Addison's disease and Simmonds' disease. Chronic constrictive pericarditis may cause atrophy of the heart and mitral stenosis, atrophy of the left ventricle only.

Among South African Bantus who live in cities, a form of heart disease occurs that is attributed to a qualitatively inadequate diet with lack of animal protein, imbalance of amino acids and disproportionately large intake of carbohydrates. All chambers of the heart are dilated and mural thrombi are sometimes present in the right atrium. Microscopic examination shows intracellular and interstitial edema and interstitial fibrosis. Most patients also have cirrhosis of the liver either with or without generalized deposits of hemosiderin. Clinically heart failure is evident (Higginson *et al.*, 1952). Vitamin B₁ has no beneficial effect, but a good and varied diet may lead to improvement (Brinkman, 1952).

Nutritional Deficiency Diseases

The human heart is affected in thiamine (vitamin B₁) deficiency and potassium deficiency (Folliis, 1948) and possibly in scurvy. In animals, the evidence indicates that the heart may be affected when the diet is deficient in any of the following: vitamins B₁, C and E, potassium and copper.

"Beriberi Heart." Deficiency of Thiamine or Vitamin B₁. More often than in any other vitamin deficiency, myocardial changes are found in vitamin B (thiamine) deficiency. Mebius (1929) believed that hydropic degeneration of the heart muscle fibers is the primary change in beriberi. The right ventricle (pulmonary conus) is particularly involved. There is also some edema present, with only a few leukocytes in perivascular locations. Keefer (1930) noted dilatation of the right ventricle of the heart with fatty infiltration and moderate degeneration of the muscle fibers. Wenckebach (1934) also emphasized dilatation of the right ventricle, particularly in the region of the pulmonary conus.

The right atrium was likewise greatly dilated, and there was interstitial edema of the myocardium. He also remarked on sarcocytolysis of the muscle fibers. This is described as giving the appearance of swelling and liquefaction to the entire muscle fiber. Despite the swelling of the sarcoplasm, the striation may still be present. The interstitial edema is identical with that described by Eppinger and associates (1935) as "serous inflammation." The absence of any vestige of inflammation is also emphasized, in spite of the observation of Rossle (1934) who attributed sclerosis of the myocardium to serous myocarditis in a case of scurvy.

Crossly the heart is described as being globose with marked dilatation affecting predominantly the right ventricle, the wall of which may measure as much as 7 mm. in thickness. In adults, the heart frequently weighs 500 or 600 grams. The average weight reported by Dock (1940) was 629 grams. Edema, hydropic degeneration and slight scarring occur particularly in the subendocardial muscle fibers and the conduction bundle, and there may be marked edema of the interstitial connective tissues. Despite the edema and hydropic degeneration of the heart, the water content is said to be the same as that of normal hearts (Weiss and Wilkins, 1937). Fatty degeneration also has been reported and, according to Dock (1940), mural thrombi are constantly attached to the trabeculae carneae of the ventricles. The cases of occidental beriberi which Weiss (1940) studied showed simple dilatation in some instances and hypertrophy in others. The reason for the dilatation or hypertrophy is unknown, as there is no hypertension in beriberi.

Weiss and Wilkins (1937) remarked that of the vitamin deficiencies, lack of vitamin B₁ is the most important cause of cardiac disturbances. They stated that the myocardial disturbances reported in rickets and scurvy may be caused by a simultaneous deficiency of vitamin B. The myocardium shows hydropic degeneration of the muscle fibers involving also those in the conduction system and there is an increase in the intercellular substance but no alteration in water content. Intercellular edema is to be noted. The same authors also found that in nine of 30 patients the

heart showed an increase in weight and considerable dilatation of cardiac chambers, particularly of the right ventricle. Histologically, they found hydropic degeneration of myocardial fibers, swelling of collagen, perivascular edema and separation of myocardial bundles. It was also emphasized that the histologic changes were not regular, specific or even characteristic of beriberi.

The microscopic lesions in the myocardium have been summarized by Follis (1942). These lesions have been described in rats, dogs, foxes and swine. Swank and Bessey (1942) observed myocardial changes also in pigeons. Most changes may be found in the hearts of swine. There is vacuolization and hyalinization of the muscle fibers followed by necrosis. Later polymorphonuclear leukocytes and mononuclear cells are found. Both the atrial myocardium and the ventricular myocardium are involved, and eventually scar tissue is formed.

Ashburn and Lowry (1944) remarked that both atria were involved in the majority of their animals with thiamine deficiency. Follis and associates (1942) observed that the heart muscle changes are quite similar to those observed in animals deficient in potassium. Blankenhorn and associates (1946) found degenerative changes in the muscle fibers, and interstitial edema in their 3 autopsied cases of occidental beriberi heart disease. Alleman and Stollerman (1948) also reported myocarditis in an instance of beriberi heart disease. Microscopic sections showed extensive cloudy swelling, loss of striations, fragmentation and fatty degeneration of the muscle fibers, and necrosis. There was also marked interstitial edema with small lymphocytic and leukocytic infiltrations. While the pathologist's impression was "subacute myocarditis of unknown origin," Alleman and Stollerman believe these changes to be consistent with the irreversible damage of chronic beriberi heart. Follis and associates (1942), however, found that myocardial necrosis in rats on a low-potassium diet may be prevented by thiamine deficiency. In this connection they also stated that no anatomic lesions have been observed in the striated muscles of thiamine-deficient animals; however, foci of necrosis have been produced in rats in which there is a concurrent potassium and thiamine deficiency.

Rinehart and associates (1947) stated that major interest in thiamine deficiency has revolved

about its effect on the heart, and that accumulated clinical and experimental evidence leaves little doubt that such deficiency results in a functional and structural defect. They found the right side of the heart to be dilated, at times appearing as if the muscle was stretched. Histologic examination revealed small foci of myocardial necrosis, as previously found in experimental thiamine deficiency in pigeons, rats and pigs. Another lesion was a well defined hydropic degeneration of myocardial fibers with hyperplastic nuclear changes, involving particularly subendocardial fibers, presumably of the conduction system. This lesion resembles that described by Wenckebach (1934) in human beriberi.

Microscopic necrosis has been reported in experimental thiamine deficiency in the following animals: swine, pigeons, dogs, rats (predominantly in the atria) and rhesus monkeys (Follis, 1948; Rinehart and Greenberg, 1949). The individual muscle fibers lose their striations and become hyaline and necrotic. Depending upon how long the animals survive, there is lymphocytic infiltration and fibrosis, the scar tissue replacing destroyed muscle fibers. In most animal species, these changes seem to affect the ventricles first, but terminally all chambers may be severely involved.

Scurvy. Deficiency of Vitamin C (Ascorbic Acid). It is known that children who have severe scurvy may die suddenly. Available but incomplete evidence indicates that this sudden death may be due to hypertrophy of the heart, especially of the right ventricle. The cause of the hypertrophy is unknown. In 1918 Erdheim observed that hypertrophy of the right ventricle was present in about two-thirds of children dying of scurvy and that when the disease was severe both ventricles might be enlarged. No histologic studies were made in this respect. Wolbach (1937) stated that degeneration of the cardiac muscle might occur. Follis (1942) described the cardiac findings in 3 infants who died suddenly of severe scurvy. At autopsy 2 of them showed hypertrophy of the right atrium, but careful histologic study revealed nothing of note.

Experimentally various lesions have been attributed to deficiency of vitamin C. Fatty changes

in the myocardium of pigs have been described by Bessey and associates (1934). Degenerative changes in the myocardium have been reported by Wnibach (1937), as well as along the line of closure of the cardiac valves in guinea pigs (McBroom *et al.*, 1937). Nonspecific valvulitis, myocarditis and pericarditis have been observed in guinea pigs by Taylor (1937). Rinchart and Mettler (1934) studied the combined effect of scurvy and beta streptococcus infection in guinea pigs and observed lesions in the heart valves and myocardium which resembled Aschoff nodules.

Deficiency of Vitamin E. Rats having deficiency of vitamin E for long periods show extensive scarring of the myocardium (Mason and Emmel, 1945). The initial lesion is excessive deposition of ceroid in the myocardial fibers. This is followed by necrosis. Connective tissue is increased and numerous macrophages filled with ceroid pigment are embedded in the collagen of this connective tissue.

Bragdon and Levine (1949) described actual foci of acute myocarditis in 15 of 17 rabbits that developed severe muscular dystrophy on vitamin E-deficient diets. In some instances, they also encountered foci of acute necrosis.

Deficiency of Potassium. The effects of hypokalemia on the heart were first observed in 1937 in rats and have since been observed in other experimental animals—mice, cats and pigs but not dogs, and in man (Follis, 1948; Macpherson, 1956). In all species the changes are essentially the same: degeneration and death of muscle fibers; phagocytosis of the necrotic material; and collapse, but not destruction, of the supporting connective tissue and reticulum framework of the heart. The lesions are seen throughout the myocardium, including the atria, but are most severe in the subendocardial portions of the ventricles and especially in the papillary muscles and

trabeculae. Large lesions are uncommon in the depths of the muscle. The endothelial cells overlying the lesions become cuboidal and crowded but the endocardium is always intact and thrombi do not form. In experimental animals the earliest lesions appear at the end of the first week of potassium depletion and consist of swelling and loss of striation of individual myocardial fibers. Cytoplasmic vacuoles that contain neither fat nor glycogen may appear and the nuclei undergo pyknosis and karyolysis. Macrophages rapidly appear and a little later fibroblasts, but it is said that these do not develop into fibrocytes or form collagen. The stroma collapses but is not destroyed, even in the late stages. A striking feature is the appearance of glycogen in the damaged muscle fibers (French, 1952). Fat does not accumulate. As the hypokalemia progresses, the function of the heart muscle is impaired as shown by changes in the electrocardiogram (low voltage, disappearance of T waves and spreading of the QRS complex) and intracellular deposits of glycogen. In rats, administration of sodium aggravates the lesions while restriction of sodium retards the myocardial damage.

McAllen (1955) reported hypokalemia in 2 patients in whom the characteristic lesions just described were found at autopsy. One patient had idiopathic steatorrhea and the other, chronic ulcerative colitis. Both had well-documented severe and prolonged deficiency of potassium; in one patient the potassium content of the heart after death was greatly reduced. Other examples in persons have been reported (Rodriguez *et al.*, 1950; Keye, 1952).

In adult cattle suffering from copper deficiency, the heart may be the seat of extreme fibrosis which is attributed to atrophy of the muscle fibers owing to longstanding anoxemia (Bennetts *et al.*, 1942). This is known as "falling disease" of cattle.

PIGMENTATIONS OF THE HEART

Endogenous Pigmentations

The heart may be pigmented in any disease in which the body is diffusely pigmented.

Hemosiderin. Deposits of hemosiderin,

usually of microscopic size, may occur in areas of necrosis, such as infarcts and abscesses, or following trauma.

Hemochromatosis. The heart is involved in hemochromatosis in approximately 90 per

cent of cases (Sheldon, 1935). The extent is variable and usually there are no gross alterations of the organ except for the brown discoloration. Sometimes the heart is small and the muscle soft. No gross changes have been recorded in the valves of the heart or the coronary arteries.

Hemosiderin is found constantly in the muscle fibers in nearly all cases. The pigment is usually spread evenly through the organ. The pigmentation may be so great that the muscle fiber appears as a sac completely filled with pigment. Fine granules are first deposited at both poles of the nucleus; from these the pigment spreads longitudinally through the muscle fiber. On cross section the granules are most numerous in the center of the fiber and least numerous at the periphery. (See Figure VII-14.) Degenerative changes, such as slight cloudy swelling and fatty degeneration may occur. Occasionally, fibrous connective tissue is increased.

Keschner (1951) found the amount of iron in the myocardium of the left and right ventricles

increased 2 to 19 times normal (33.5-38.3 mg. per 100 grams of dry tissue) in 11 patients with hemochromatosis, including 2 with exogenous hemochromatosis or transfusional siderosis, in one of whom the highest value was found. Various degenerative changes of cardiac muscle were associated with the high concentration of iron—disproportion of sarcoplasm to myofibrils, fragmentation and separation, pigmentation of fibers, hypertrophy of fibers, nuclear displacement, pyknosis and karyorrhexis, cloudy swelling, vacuolar and hydropic degeneration. Fibrosis of varying degree was present in 9 of 11 hearts but did not correlate with the amount of pigmentation. When stained by Gomori's method, the iron pigment appeared as dustlike blue particles or coarse granules. Hemosiderin appeared to be laid down in a bipolar spindle formation around nuclei and to spread longitudinally through the myocardial fibers. The connective tissues contained scant hemosiderin.

The cytologic sequences have been studied by Theret (1955) who described the first change as deposits of ferruginous pigment on the dark Q disks of the myofiber. The fiber increases in size and eventually ruptures. The connective tissue contains round cells and histiocytes and shows

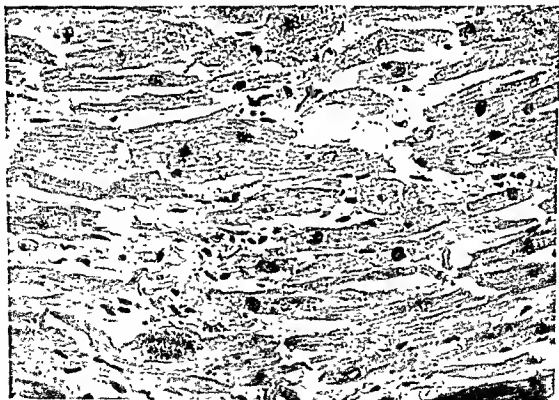


Figure VII-14. Hemochromatosis. Note deposits of hemosiderin and degeneration of myocardial fibers. Patient was a 59-year-old man with hemochromatosis, who died of heart failure. X-400. (WCGH, 40 A 407.)

edema and fibrosis. Theret felt that the profound alteration of the fibrillar macromolecules is caused by hormonal disturbances and results in heart failure.

According to Keschner (1951), the changes in the heart are the same in hemochromatosis and transfusional hemosiderosis, however, Kleckner and associates (1954) observed changes in the myocardium of only one of 16 patients with transfusional hemosiderosis. In hemochromatosis they found myocardial involvement in 13 of 18 cases.

Hemofuscin also is found chiefly in the myocardial fibers where, like hemosiderin, it accumulates adjacent to the poles of the nucleus. This pigment is also found, both free and within phagocytes, in the vessel walls and the connective tissue of the interstitial tissues. It is not found in the endocardium, save for a small amount in an occasional phagocyte.

Bile Pigment. Bile pigment may be found in the myocardial fibers in patients suffering from jaundice. The pigmentation may lead to the development of cloudy swelling and fatty degeneration. It produces diffuse pigmentation of the sarcoplasm and is best demonstrated in unstained frozen sections.

Lipochrome Pigment. Small amounts of lipochrome pigment may be deposited at the nuclear poles of the myocardial fibers in the

form of yellow or yellow-brown granules. It is thought to be exogenous and to be introduced with foods (Connor, 1928). It may occur in association with brown atrophy of the heart.

Missmahl (1950), utilizing polarization microscopy, detected the presence of lipids directed at right angles to the longitudinal axis of the myocardial fiber. He believed them to be lipofuscin and similar to the substance isolated by chemical means by Heidenreich and Siebert (1955). These workers, using isolated homogenates of cardiac muscle, characterized lipofuscin as having a concentration of the dried substance of 20 per cent fat, 11.8 per cent nitrogen, and 0.424 per cent phosphorus. Studies of ultraviolet absorption revealed benzol rings, and paper chromatography revealed amino acids typical for protein. The pigment contains 0.0312 per cent iron, shows minimal esterase activity and contains one-tenth as much cathepsin as the pancreas. Histologically the pigment is in the form of round granules that stain with Sudan III and Scharlach R but are not acid-fast.

Exogenous Pigmentation

The heart may be pigmented in silver poisoning, and occasionally deposits of anthracotic or silicotic pigment are found in the pericardium and interstitial tissues of the heart in cases of severe anthracosis and silicosis.

THE HEART IN ENDOCRINE DISEASES

Acromegaly

Usually patients with acromegaly die of cardiac failure and at autopsy the heart is frequently large. It is thought that hypertrophy results (a) as part of the general splanchnomegaly and (b) from the increased work required to supply blood to the enlarged body (Courville and Mason, 1938). The enlargement is greatest in the long axis. Histologically hypertrophy of muscle fibers and diffuse interstitial fibrosis may be so marked as to cause visible scarring (Cushing and Davidoff, 1927).

From a study of 21 patients, with 4 autopsies, Hejtmancik and associates (1951) concluded that the frequency of cardiac failure resulted from a

combination of malfunction of the enlarged fibers, hindrance to contraction and to transmission of impulse caused by extensive fibrosis, and impaired metabolism when diabetes or thyrotoxicosis was also present. The incidence of hypertension was not increased in their patients; but when hypertension was present, it was poorly tolerated.

Hyperthyroidism

There is a rather extensive literature on myocardial changes in hyperthyroidism, and many studies have been undertaken to determine if feeding with desiccated thyroid or thyroxin will produce changes in the heart muscle.

Some of these references may be found in

Saphir's (1942) review. Goodpasture (1921) reported the cardiac findings in 2 patients who evidently died of myocardial exhaustion. Microscopically, edema and focal necrosis were encountered. Willis and co-workers (1923) stated that histologically the myocardium of 18 patients showed swollen fibers with indistinct striations as well as marked fatty changes. Myocarditis was not mentioned. Lewis (1931), from a study of 12 necropsies of patients with hyperthyroidism, concluded that the changes in the heart were characterized by hypertrophy, dilatation and moderate fibrosis of the myocardium, that the cardiac damage may be fairly severe and that the cardiac disorder could not be relieved by treatment. There may also be toxic necrosis in the myocardium caused by toxic thyroid secretion. He suggested that the increased work demanded from the heart results first in dilatation, then in hypertrophy, and renders the heart more susceptible to secondary noxious influences. There was no interstitial connective tissue increase and no cellular infiltration. McEachern and Rake (1931) studied the findings in all cases of hyperthyroidism coming to autopsy at the Johns Hopkins Hospital since 1899. There were 27 cases. In 14 instances the hearts were grossly normal. In 8 instances they found moderate perivascular or intermuscular fibrosis or small foci of round cell infiltration. Cardiac hypertrophy was noted in 16 of 27 hearts. No relationship could be established between the incidence of atrial fibrillation or the duration of hyperthyroidism and the ultimate cardiac lesions.

Rake and McEachern (1931) studied the pathologic changes in the heart and other tissues of animals with hypertrophy induced by thyroxin. The cardiac changes in the animals with hyperthyroidism were insignificant, and varied but little from changes seen in the normal control animals. It was concluded that no significant alteration had been produced by hyperthyroidism. Subsequently, Rake and McEachern (1932) stated that postmortem and experimental material indicated that hyperthyroidism itself produces no specific lesions in the myocardium. They believed that the damage produced by physiologic wear and tear on the one hand, and by any associated infection or disease on the other hand, tended to be more accentuated in the patient with hyperthyroidism than in the normal person. The evidence did not suggest the occurrence of a specific toxin producing specific myocardial lesions. It was felt that too much emphasis had been placed in the past on the morphologic changes in the

myocardium with consequent neglect of important alterations in the metabolism and the function of the muscle fibers. These authors also suggested that perhaps the absence of glycogen in the cardiac muscle in hyperthyroidism renders the myocardium liable to injury, and that it reacts by diminished function. In this connection, it may be mentioned that McDonald and associates (1938) concluded that in hyperthyroidism, cardiac failure was not contingent on the presence or absence of glycogen. The function of cardiac glycogen was not primarily to produce energy, but, in some unknown manner, to act as a stabilizer between the conservation of energy and its expenditure. Likoff and Levine (1943) stated that it is apparent that thyrotoxicosis is not infrequently the sole cause of congestive heart failure. They did not, however, give a microscopic description of the cardiac findings.

In summary, as White (1951) has stated, there is no constant cardiovascular lesion in thyrotoxicosis. In a few cases necrosis of the myocardium has been found, but this finding has not been confirmed as a thyroid effect. In severe thyrotoxicosis the weight of the heart is generally increased.

Hypothyroidism

Higgins (1936) commented on the confusion in the literature concerning cardiac lesions in myxedema.

He pointed out that some authors had expressed the belief that the changes were part of the hypothyroid state while others have indicated that they were incidental. He also mentioned that at the Massachusetts General Hospital in Boston only 5 autopsy records indicated changes in the heart in myxedema. Four of these referred to interstitial edema with more or less fibrosis of the heart muscle fibers and one, to fibrosis only. He believed that in the early stages of thyroid deficiency there is a mucoid infiltration of the muscle fibers which can be overcome by the use of thyroid extract. As the disease progresses, further degenerative changes occur, the heart becomes larger and coronary sclerosis develops. Because of these early and late changes, degeneration of the muscle fibers occurs and is followed by extensive fibrosis of the myocardium. He concluded that the condition of the heart in myxedema is a distinct clinical and pathologic entity and should be considered in the differential diagnosis of every obscure cardiac disease. Gordon

(1935) expressed the view that the clinical features of "myxedema heart" were produced by pericardial effusion in the course of myxedema.

Webster and Cooke (1936) studied morphologic changes in experimental myxedema in rabbits. Microscopically, the heart muscle fibers from the myxedematous animals did not take the hematoxylin-eosin stain as well as those from the normal control animals. There was a striking increase in the size of the spaces between the individual fibers. The fibers themselves were swollen, and the number of fibers per square millimeter was decreased. There was increased prominence of the longitudinal striations with partial disappearance of the transverse striations. The nuclei were pyknotic and surrounded by clear spaces. The increase in the perinuclear space was shown clearly in a cross section of the muscle bundle. Frozen sections stained with Sudan IV showed that there was little fat in the heart muscle and no fat in the clear spaces around the nuclei and between the fibers. The authors stated that the heart muscle of these myxedematous animals had an average fluid content of 81.9 per cent, compared with 75.6 per cent in the control series. They concluded that myxedema was apparently capable of producing serious myocardial damage in the adult rabbit. It must be noted, however, that they terminated their experiments by killing the animals with carbon monoxide (illuminating gas) which also produces definite changes in the myocardium (see pages 528 and 529).

Marzullo and Franco (1939) reported the occurrence of myxedema in a patient who died suddenly. The heart grossly and microscopically showed a normal myocardium. White (1951) stated that the occasional finding in myxedema of a well marked cardiac enlargement has led to the term "myxedema heart." He believes that the enlargement is the result partly of the dilatation and partly of the myxedematous change affecting the heart tissue. (See also Schnitzer

and Gutmann, 1946.) La Due (1943) presented the autopsy findings of a 52-year-old woman with myxedema who died of heart failure. The heart was enlarged and dilated, weighing 400 grams. Microscopically, the sarcoplasm of many heart muscle fibers was completely replaced by hydropic vacuoles. An edematous material was also present between the heart muscle fibers but there were no cellular elements. These changes were more striking just beneath the endocardium.

Brewer (1951), from histochemical studies of the tissues of a patient who died of myxedema, concluded that the infiltrations in the skin and tongue were probably a mixture of mucoproteins containing hyaluronic acid and chondroitin sulphuric acid, but that in the heart the infiltrations consisted of a histochemically distinct mucoprotein that is only weakly acid. He found that the mucoid deposit in the myocardium stains with periodic acid-Schiff reagent (PAS) and slightly with Ehrlich's hematoxylin but does not show metachromasia with toluidine blue and does not take up methylene blue at a pH that is more acid than 5. The material is not glycogen since it is not removed by saliva, diastase or hyaluronidase. It gives a negative Feulgen reaction and does not stain with mucicarmine or Sudan Black B. In contrast, the deposits in the tongue stain deeply with hematoxylin and PAS and are strongly metachromatic and strongly acid, taking up methylene blue at pH 2.5. The metachromasia at the periphery of the deposits is reduced by hyaluronidase but not by diastase.

Thus, in summary, it appears that there is no specific change within the myocardium which would warrant a diagnosis of either *myocarditis* or "myxedema heart." Changes similar to those occurring in the subcutaneous tissue or muscle tissues throughout the body may also be present in the myocardium.

ATROPHY OF THE HEART

Atrophy of the heart may be defined as a decrease in the size of the heart after it has acquired partial or full growth. In contrast to this is the congenitally small size of the heart, which is called *cardiac hypoplasia*. Atrophy is the result of ischemia and inadequate nutrition. Hence, it is common to find

not only simple reduction in the size of the fibers, but also evidences of cellular injury such as cloudy swelling, fatty degeneration, pyknosis and even necrobiosis and lysis. The changes are thought to be brought about by enzymatic liquefaction of tissue proteins with formation of the same products which appear

after hydrolytic cleavage of protein in the digestive tract, namely peptides and amino acids (Bradley, 1938).

The heart is reduced in size, frequently to two-thirds or one-half of normal. The apices of the papillary muscles are quite fibrous and the papillary muscles, especially of the left ventricle, are short and narrow so that the interpapillary spaces are pointed. The epicardium and the endocardium may be wrinkled and thick.

Microscopically the myocardial fibers first become smaller and then completely disappear, probably by autolysis (Karsner *et al*, 1925). The reduction in the size of the heart is the result of reduction in both size and number of the muscle fibers (Figure VII-15). They tend to become uniform in breadth, and large fibers disappear. The nuclei are also small and lie closer together than they do normally. The number of nuclei in the atrophic heart is greatly increased in proportion to the number of fibers. There is also a relative increase in purine nitrogen. Frequently there is increased basophilia, but it is not known whether this is due to an actual increase in desoxyribonucleic acid or merely to condensation. No increase in mitoses occurs.

In *brown atrophy* there is striking accumulation of yellow-brown, granular pigment in the sarcoplasm, usually at the nuclear poles, about which it forms spindle-shaped figures. This pigment does not contain stainable iron. It is said to be largely hemofuscin associated with small amounts of hemosiderin (Connor, 1928). There is both relative and absolute increase in the amount of pigment. In severe cases the granules may be found not only within the muscle fibers but also scattered between them, probably as the result of destruction of myocardial fibers. The cement lines of the myocardial fibers are usually more distinct than normal.

Atrophy may also occur in a heart that was formerly hypertrophic. This is particularly common in emphysema or in coronary atherosclerosis and in such cases the weight of the heart may be either within or above normal limits.

Atrophy of the heart may be seen in starva-

tion, senility, as the result of endocrine disturbance, and especially as the result of wasting diseases such as tuberculosis and malignant tumors. The atrophic heart is usually regarded as having a decreased reserve power.

In a series of 2000 consecutive autopsies, Hellerstein and Santiago-Stevenson (1950) found 48 hearts with brown atrophy (average age of patients, 62 years) and 41 with simple atrophy (average age, 42 years). Atrophy was associated with a neoplasm in 73 per cent of the 89 cases and with chronic infection in 16 per cent. The average weight of the heart was 219 grams (99-300 grams) and there was a relatively greater loss of weight in the heart than of the body in general. The consistency of the myocardium was firmer in brown atrophy than in simple atrophy.

Serous (Gelatinous or Mucoïd) Atrophy of Subepicardial Fat

Subepicardial fat may undergo a peculiar degenerative change which appears to be a combination of atrophy and edema. It is usually found in emaciated subjects suffering from senility or long-standing wasting diseases, such as tuberculosis or cancer. The fat



Figure VII-15 Atrophy of myocardium showing greatly reduced size of the fibers and hyperchromatic nuclei. Hematoxylin and eosin X240.

is converted into a brown or red-brown, translucent, wrinkled mass which looks gelatinous (Figure VII-16). Usually the coronary arteries are tortuous because they do not participate in the atrophy. Microscopically the fat cells are distended with small droplets, which are often yellow-brown in color, and

lie in the edematous ground substance of the pericardium. The individual cells undergo considerable alteration in size and shape so that many of them are round, spindle- or star-shaped. Indeed, the cells may become so small that they finally resemble fibrocytes.

EFFECTS OF DRUGS AND POISONS ON THE HEART

The lesions commonly seen in the human heart following poisoning or drug intoxication consist of cloudy swelling or fatty degeneration of the myocardium, focal hemorrhages which are usually endocardial or epicardial but sometimes myocardial and, in more severe damage, focal myocardial necrosis. Cellular exudates occur in some instances, usually about necrotic foci, and consist principally of lymphocytes and mononuclear cells. Occasionally the cellular component is the major feature of the microscopic picture. If the poisoned individual survives long enough, the necrotic foci may undergo healing by fibrosis. Cardiac dilatation is some-

times conspicuous and, if the toxic substance also causes pulmonary injury with obstruction of blood flow through the lungs, the dilatation may be predominant in the right ventricle (Petri, 1930).

It is evident from the preceding description that the cardiac lesions are nonspecific. In no instance are they pathognomonic of any one poison or drug. A few compounds, however, do cause sufficiently uniform lesions to be noteworthy. Thus *cadmium*, and especially *phosphorus*, usually cause severe fatty degeneration of the myocardium. *Benzol* or *salicylate* poisoning usually cause endocardial and epicardial hemorrhages. *Arsenic* compounds cause endocardial hemorrhages which are likely to be broad or flame-shaped and to be located on the left side of the interventricular septum. *Mercury* poisoning often results in deposition of calcium in myocardial fibers. Acute *carbon monoxide* poisoning makes the heart bright red (Gonzales *et al.*, 1954).

A drug or poison may injure the heart either by direct action on the myocardium or other cardiac tissue or indirectly by injury elsewhere in the body. Such structures as brain, lungs, liver, kidneys, bone marrow, and alimentary tract are common sites of injury by drugs and poisons. Major damage to one or more of them may result in anoxemia, electrolytic imbalance, accumulation of metabolic products, or infection. Since the cardiac lesions described are nonspecific, it is often impossible to attribute a given lesion to direct cardiotoxic action. The relevance of observations made in experimental animals may depend greatly upon the methods and the species employed. Examples of cardiac lesions



Figure VII-16. Serous atrophy of fat. Patient was a cachectic 46-year-old man who died of lymphoblastoma. (WCGH, 44 A 52.)

produced at least in part by direct action of a toxic substance are fatty degeneration caused by phosphorus, cadmium, and the mushroom *Amanita phalloides*; injury to cardiac capillaries by inorganic arsenic; and inactivation of myocardial respiratory enzymes by cyanide compounds. In many other instances, the observed lesions may be explained principally as the result of indirect causes of which anoxemia seems often to be the most important.

Carbon monoxide causes cardiac ischemia by combining with hemoglobin and reducing its capacity to carry oxygen. Patients dying within a few days of exposure to a high concentration of the gas, present pericardial and subendocardial hemorrhages. The latter are conspicuous in the left ventricle, and especially in the papillary muscles. Microscopically one may find focal fatty degeneration and necrosis of muscle fibers, and an abundant cellular exudate consisting mostly of polymorphonuclear leukocytes (Gurich, 1925, Walcher, 1939).

In a patient who died 13 days after exposure, Neuberger and Clarke (1945) found multiple foci of myocardial necrosis, chiefly subendocardial, and occasional petechial hemorrhages in otherwise intact areas of myocardium. Ehnich and associates (1944) found similar lesions in dogs. Beck and Suter (1938) pointed out the frequency of coronary thrombosis in patients who had recovered from exposure to carbon monoxide and emphasized the possibility of permanent cardiac damage after acute intoxication. Holm (1950) encountered severe myocardial fibrosis in a patient who developed cardiac failure after carbon monoxide poisoning and died 4 years later.

Drugs commonly employed for the treatment of cardiovascular disease, such as adrenalin, atropine, digitalis, quinidine, and thiocyanates, have not been shown conclusively to cause morphologic changes in the human heart.

Experimentally, in sufficient dosage, lesions can be produced in animals. Dearing and associates (1943a) found no myocardial lesions in cats when they gave doses of digitalis preparations calculated to be the equivalent of therapeutic

doses in man. In a few instances, doses twice as great (equal to 60 per cent of the minimum lethal dose) caused focal myocardial degeneration and necrosis with surrounding hemorrhages and cellular infiltration. The lesions seemed to have a predilection for the papillary muscle of the left ventricle and the interventricular septum. Healing occurred by fibrosis. In subsequent experiments in dogs, toxic doses of digitalis preparations reduced the coronary blood flow for a few hours, but myocardial lesions were not attributed to the diminished blood flow (Dearing *et al.*, 1943b). Kyser and associates (1946) found that the cardiotoxic effects of digitalis in dogs were modified by aminophyllin, theobromine sodium acetate, and atropine sulfate but not by papaverine hydrochloride.

Experimentally in rabbits, injections of adrenalin have been followed by focal myocardial hemorrhages, degeneration, necrosis and lymphocytic infiltration, and later by replacement fibrosis and by hypertrophy.

Raab (1943) reported sudden death of a young athlete in whom at autopsy no lesion was found; chemical examination of organs for alcohol and poisons also was negative. An excessively high concentration of adrenalin-like substances was found in the heart muscle and was believed to be the immediate cause of death.

Acute poisoning by alcohol produces the same lesions caused by other respiratory depressants. In chronic alcoholism the changes are attributable, not directly to the alcohol, but rather to the accompanying state of nutrition. Hence, one may find marked fatty infiltration in persons who have maintained a high caloric intake of food in addition to the alcoholic beverages consumed; on the other hand, if food intake has been inadequate, the changes described in nutritional deficiencies may be present.

Hypersensitivity to drugs may result in pronounced myocardial lesions. Lesions have been noted particularly in hypersensitivity to certain organic arsenical compounds and to sulfonamides. Such reactions have a large inflammatory component and are dealt with in the Chapter on Myocarditis.

EFFECT OF IONIZING RADIATION ON THE HEART

Warren (1942) has reviewed the effects of ionizing radiation on the heart. The severity of the changes depends largely on the amount of irradiation to which the subject is exposed. If we summarize numerous reports in which various amounts of irradiation were administered to experimental animals such as the dog, rat, rabbit, and sheep, the changes observed have included hyalinization of pericardial and epicardial connective tissue, edema, atrophy, and necrosis of myocardium; proliferation and hyalinization of interstitial tissue of the myocardium, focal lymphocytic and perivascular mononuclear and polymorphonuclear infiltration; perivascular edema, hemorrhage, and hyalinization; and vascular thickening. Prosser and associates (1947) reported electrocardiographic abnormalities and evidence of cardiovascular failure in animals exposed to irradiation and in acute cases, at autopsy, cardiac hemorrhages of varied size and location. Coon and associates (1955) have observed a loss of potassium from the heart of the rabbit and of the dog shortly following moderate doses of γ -radiation.



Figure VII-17. Epicardial hemorrhages resulting from exposure to ionizing radiation. (Courtesy, Armed Forces Institute of Pathology, Neg. HS 307 A.)

In radiation therapy in man, according to Warren, little radiation reaches the heart unless treatment is directed at a thoracic or left mammary tumor, at the lower mediastinum, or at the esophagus. In 10 patients who received irradiation that included exposure to the heart, who lived two days to a year after treatment, Thibaudeau and Mattick (1929) observed changes ranging from slight interstitial fibrosis to hyaline and fatty degeneration and necrosis of the myocardium. Sometimes round cell infiltration was encountered. In other cases, granular and vacuolar degeneration of the myocardium and hyalinization have been stressed. Warren pointed out that, as elsewhere in the body, "the various forms of cardiac damage secondary to radiation therapy cannot be recognized as specific in themselves, but the aseptic necrosis, hyaline fibrosis, and obliterative vascular changes combine to form a fairly characteristic lesion."

Tricot and associates (1954) reported an instance of constrictive pericarditis which they thought was the result of x -radiation (total of 13,000 r delivered to the precordium over a period of 10 years) in treatment of metastatic carcinoma of bone, primary in the breast.

In swine exposed to total body irradiation from an atomic bomb explosion (Bikini) and dying one to 29 days later, the cardiac muscle rarely showed any evidence of injury, even hemorrhage being absent (Tullis, 1949).

Liebow and associates (1949) have described the effects on man of the atomic bomb explosions at Hiroshima and Nagasaki. In patients dying within 14 days of the explosion, epicardial petechiae (Figure VII-17) were common and there was occasional edema about myocardial vessels. Similar changes were present in patients surviving to the seventh week, and in addition there were occasional endocardial and perivascular myocardial hemorrhages. In some instances there was subendothelial and myocardial exudation

of plasma cells and small and large mononuclear cells. In 33 patients who died more than 6 weeks after the explosion, there were

no significant cardiac changes except for focal hemorrhages and one instance each of "fatty change" and "focal necrosis."

EFFECT OF DISEASES OF BLOOD ON THE HEART

Anemia

The heart may become dilated and hypertrophic in severe chronic anemia.

Porter (1937) found roentgen evidence of cardiac enlargement in 14 patients with hookworm anemia, and Ellis and Faulkner (1939) found such evidence in 20 of 38 patients with anemia of various causes. With effective treatment the heart may become smaller but may never return to normal size. Porter ascribed the rapid reduction in cardiac size in treated patients to disappearance of dilatation, and thought that residual enlargement represented hypertrophy. In one of his patients who died of heart failure while under treatment, the heart weighed 650 grams. Cabot and Richardson (1919) found the heart heavier than normal in all but one of 19 patients who died of pernicious anemia.

In addition to enlargement, fatty degeneration of the myocardium is common in severe anemia. The myocardium is flabby and shows characteristic yellow subendocardial streaking. According to Friedberg and Horn (1939) focal myocardial necrosis may be prominent in young persons dying with severe anemia following gastrointestinal hemorrhage.

Formerly pernicious anemia and chlorosis were the usual forms of anemia causing cardiac lesions, but these have been superseded in recent years by sickle cell anemia and secondary anemias. Winsor and Burch (1945) have especially emphasized the frequency with which sickle cell anemia causes cardiac disease.

Two possible factors in the production of the cardiac lesions seen in anemia are diminished oxygen supply to the heart and cardiac overwork. There is no doubt that anemia results in anoxemia, and that anoxemia of similar degree from other causes can produce lesions like those described. While it is clear that anoxemia is an important factor, the significance of overwork is uncertain.

Because cardiac output is increased in anemia, it might be supposed that the heart must do more work. Anemia is also accompanied, however, by vasodilatation and by reduced blood viscosity, and these tend to lessen cardiac work. How far these two factors counteract each other has not been established, hence, the role of overwork in producing the changes seen in anemia is uncertain.

Anemia by itself rarely causes congestive failure and it is doubtful if it ever causes fatal heart disease. It may, however, be an important secondary cause. In patients with pre-existing heart disease, the development of anemia may precipitate myocardial failure and, conversely, treatment of anemia may alleviate failure. Similarly, angina pectoris has been precipitated. Kinney and Mallory (1945) reported cases in which the acute anemia following hemorrhage from peptic ulcers precipitated congestive failure and myocardial infarction (see pages 584 and 592).

Polycythemia

In both primary and secondary polycythemia, there is an increase in the viscosity and the volume of the blood.

It has been thought that these changes impose a burden on the heart, leading to hypertension and cardiac failure. White (1951) stated, however, that peripheral vasodilatation largely prevents such an additional cardiac burden. Norman and Allen (1937) found that the blood pressure in patients with polycythemia was no higher than in controls, and Brown and Ciffin (1926) found no cardiac enlargement in 14 patients. Friedberg (1956) stated that heart failure is a rare complication of polycythemia unless there is associated myocardial infarction or hypertensive and arteriosclerotic heart disease. The latter conditions he regarded as coincidental. That there is an increased tendency to thrombosis in polycythemia is well known, but Norman and Allen concluded that thrombosis of coronary arteries is less common than in the vessels of other organs. In their series of 98 cases of polycythemia vera, coronary disease was encountered in 5 patients, in one of

whom a coronary arterial thrombus was found at autopsy.

Leukemia

Cardiac hypertrophy may occur in leu-

kemia. The enlargement has been attributed in part to the associated anemia and in part to the increased metabolic rate. The subject is discussed in Chapter XIII on Neoplasms.

THE HEART IN FAMILIAL DISEASES AFFECTING MUSCLE

Progressive Muscular Dystrophy. In this disease, known also as pseudohypertrophic muscular dystrophy, changes may occur in the myocardium similar to those seen in the skeletal muscles and may be associated with sudden development of fatal cardiac failure. Because of meager descriptions of the heart in most reported cases, the true incidence of cardiac involvement is uncertain; but probably it is high.

The earlier literature has been reviewed by Globus (1923). In 19 cases in which autopsies have been reported since 1922, Zatuchni and associates (1951) found the heart small in some instances, normal or enlarged in others. The range was 140 to 650 grams. Moore (1954) encountered a heart that weighed 450 grams in a 10-year-old boy, and Storstein and Austarheim (1956) a heart that weighed 750 grams in a 20-year-old man.

The appearance of the myocardium is variable. In some places it may be yellow-brown because of fatty infiltration, in others it shows gray flecks and strands of fibrous tissue. Microscopically, there is widespread replacement of muscle fibers by connective tissue and by fat of adult form. Some of the muscle fibers are hypertrophic; others are small and distorted and show fragmentation or loss of striation. The nuclei of the fibers may show degeneration. Sarcolemmal nuclei are relatively increased and there may be a sparse infiltration of mononuclear cells. Cardiac valves are normal. The endocardium is usually normal or slightly thickened, but in the case reported by Zatuchni and associates (1951) it was strikingly thickened. The coronary arteries are normal.

Dystrophia Myotonica. This disease, also called *myotonia atrophica*, is characterized by

increased tone of skeletal muscles, muscular atrophy, cataracts, baldness, and testicular atrophy. Although symptomatic heart disease is uncommon, the frequency of mild hypotension and the high incidence of conduction defects and arrhythmias have attracted clinical attention to the heart (Waring *et al.*, 1940; Evans, 1944; Kilpatrick and Caughey, 1955).

Careful postmortem examinations have seldom been reported, however, and no consistent morphologic changes have been noted.

Fagin (1946) found atrophy of myocardial fibers in a woman who also had carcinoma of the stomach. The heart weighed 275 grams. On the other hand, Fisch and Evans (1954) found diffuse fibrosis and hypertrophy of scattered myocardial fibers in a man whose heart weighed 340 grams. No abnormality was found in 5 adult hearts examined by Black and Ravin (1949). Reported weights ranged from 250 to 450 grams. The heart was also normal in 2 autopsies reported by Kilpatrick and Caughey (1955).

Friedreich's Ataxia. Schilero and co-workers (1952) summarized observations made since Friedreich (1863) described the ventricular hypertrophy and fatty degeneration of the myocardium associated with the form of cerebellar atrophy that bears his name. All chambers of the heart, but particularly the ventricles, may be hypertrophic. Microscopically there is diffuse replacement of myocardial fibers by connective tissue, and hypertrophy or fatty degeneration of remaining fibers. Usually striations are lost and nuclei are large and vacuolated, and there is infiltration of lymphocytes and eosinophils. The Purkinje fibers are also separated by connective tissue and by a sparse cellular exudate. Clinically, cardiac arrhythmias and congestive failure are common.

He found that the postmortem volume was always less than in life, but that the amount of the difference (as much as 52 per cent) was unpredictable. His results indicate that, even if normal values for postmortem cardiac volume were established, they might have little relevance to cardiac volume in life. The same consideration applies to postmortem measurement of the total capacity of the heart, which Friedman calculated to average 400 ml. in life, and to measurement of the capacity of individual chambers.

As a means of making estimates of normal heart size, there remains the volume of the cardiac tissue. Postmortem, this volume can be determined with fair precision and probably reflects accurately the volume during life. Equally useful information can usually be obtained, however, by weighing the heart. Should an estimate of volume be desired, it can be obtained from the cardiac weight and the average specific gravity, which Bardeen (1918) has reported as 1.05 and Friedman as 1.03.

There is general agreement that most adult hearts without obvious disease weigh between 250 and 350 Gm. According to White (1951), the lower limit of normal weight in adults is 200 Gm. and the upper limit 375 Gm. According to Karsner (1955), normal male adult hearts weigh between 300 and 350 Gm., and female hearts weigh about 50 Gm. less. Both authors emphasize the importance of taking body size into consideration in determining deviations from normal. The tables in Chapter XVIII list cardiac weights according to body weight, height, sex, and age. They demonstrate the impossibility of setting a single range of cardiac weight in adults which will allow for normal variability and still be consistently useful in the recognition of enlargement.

Many reports indicating a relation between cardiac weight and body size or some other factor are based on unselected autopsy cases and, therefore, are of little use in defining the size of the normal heart. Among the larger reported series, those of Smith (1928) and of Zeek (1942) (see Chapter XVIII) are notable in the care with which instances of cardiovascular disease were excluded. Zeek observed the further important precaution of estimating the reliability and varia-

bility of her data by statistical methods. In a smaller series of 187 cases, Rosalun (1941) had nearly ideal material in that it was derived only from men who died accidentally or after short illnesses and showed no gross or microscopic evidence of heart disease. He, too, dealt with his data statistically, and from them derived an equation simultaneously relating heart weight to body weight and to age. The possibility of hypertension was not excluded in the selection of cases and this factor may account both for the apparent significance of age and for a high mean value of cardiac weight (mean 355 ± 1.1 Gm.; range 210-565 Gm.). Smith and Zeek reviewed earlier work relative to age. Neither found age a factor beyond childhood in his or her own data.

The chief practical purpose of defining normal cardiac weight is to assist in the recognition of abnormal myocardial mass. At present, comprehensive data are not available on the weight of the myocardium in health which are suitable as standards for direct comparisons. A limiting factor in the usefulness of total cardiac weight is the variable contribution of epicardial fat to cardiac weight.

In his 1481 unselected cases, Müller (1883) found that from a negligible quantity in early childhood, epicardial fat came to represent 20 per cent of cardiac weight at the age of 70. There were wide variations in individuals, however, and rarely fat was responsible for half the weight of the heart. In 135 unselected patients, most of whom were elderly, Reiner and associates (1955) found that epicardial fat varied linearly with age. Heavy hearts in obese men were related more closely to myocardial weight, however, than to epicardial fat. With respect to the myocardial weight in individual chambers, Müller found that the right atrium weighed slightly more than the left, the left ventricle weighed twice as much as the right, and the combined weight of the atria was one-fifth that of the ventricles.

In the absence of suitable standards of weight, the thickness of the myocardium is commonly used as an index of the myocardial mass of individual chambers, but in dilated chambers, interpretation of the measured thickness of the wall may be difficult. (See Chapter XVIII for representative values.)

Gross Features of Enlargement. Enlarge-

ment resulting from excessive deposit of epicardial fat has been described. We are here concerned with hypertrophy of the myocardium and dilatation of cardiac chambers. These two forms of enlargement commonly occur together in all types of heart disease and almost invariably in chronic congestive failure. Which of the two predominates depends upon the location, severity, and duration of the underlying disease. In early stages of a cardiac disease, only a single chamber may be enlarged, later, all chambers may be affected. The atria are capable of greater dilatation than the ventricles; the ventricles show greater degrees of hypertrophy. Hypertrophy without appreciable dilatation is frequently seen in the left ventricle, occasionally in the right ventricle, seldom in the atria. Despite the vagueness of the borderline between normal and enlarged hearts and the limitation on quantitative measurements of cardiac size, outspoken hypertrophy and dilatation have numerous distinguishing characteristics.

Hypertrophy is most frequent in the left ventricle (Figure VII-18). Hearts so affected commonly weigh up to 500 Gm., and weights of 1000 Gm. or more are occasionally ob-

served. The myocardium is firm, frequently somewhat deeper red than is normal, and may be flecked with small pale gray scars. The endocardium is often slightly thickened and opaque. In cross-section, both the free wall and the interventricular septum are thickened (Figure VII-11), the latter somewhat less. In the absence of dilatation, the wall may appear in transverse section as a heavy ring which actually reduces the lumen of the chamber. Such hypertrophy has been called "concentric" in distinction from the "eccentric" hypertrophy seen when the chamber is also dilated. The trabeculae carneae and the papillary muscles are also enlarged and stand out prominently.

Other changes in configuration of the left ventricle in hypertrophy have been described in detail by Kirch (1921) and by Grant (1953a, b). As the wall of the chamber thickens, it also becomes longer. The elongation is proportionately greater toward the apex; the papillary muscles appear, therefore, to arise relatively nearer the mitral orifice than in the normal heart. The lengthening is greater also in the ventral and lateral portions of the ventricle (cephalad and dorsal as the heart lies in the body). As a result, these

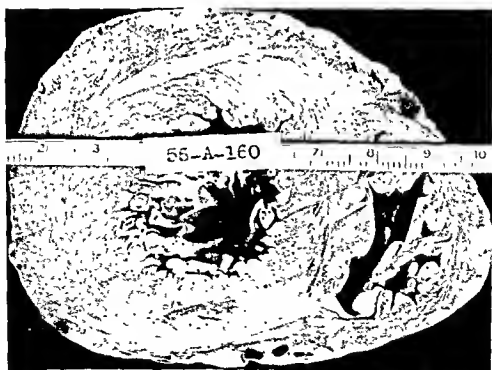


Figure VII-18. Hypertrophy of the left ventricle. The heart has been cut coronally midway between base and apex.

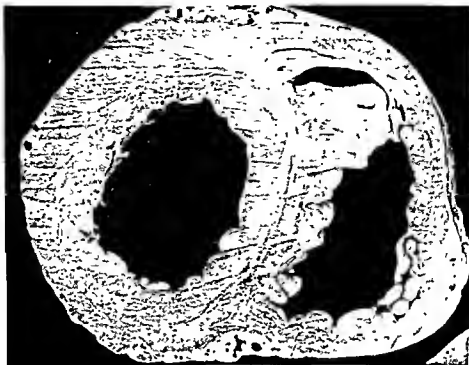


Figure VII-19. Hypertrophy and dilatation of the right ventricle (*cor pulmonale*).

portions develop a greater curvature of outline than the rest, the normal outward bulge of the myocardium about the mitral ring is exaggerated, and the ring itself is tilted to a plane more nearly parallel with that of the aortic ring. How the mitral valve accommodates itself to the lengthened chamber is not certain. Kirch's measurements indicated that the papillary muscle becomes longer, but the chordae tendineae remain unchanged. Grant, on the other hand, was impressed by instances in which the anterior leaflet showed equal elongation of all three elements of the valve. By itself, hypertrophy does not lead to any change in the orifices of the mitral and aortic valves. Just below the aortic ring, however, the normal bulging of the myocardial wall into the lumen is exaggerated, sometimes so much that it seems to have impeded the outflow of blood. It is in this location that endocardial pockets occasionally form when the hypertrophy follows aortic valvular disease. Kirch (1930) believed hypertrophy begins along the outflow tract of the ventricle and progresses "against" the blood stream along the inflow tract to the mitral orifice, but Grant was unable to confirm this observation.

Dilatation of the left ventricle usually is seen in hearts that are also hypertrophic and accentuates some of the features of hypertrophy while it diminishes others. Dilatation

affects mostly the apical portions of the lumen and, to a slighter degree, the lumen in front of the mitral valve. The portion behind the valve is least affected. The apical segment becomes less conical and more bowl-shaped. The thickness of the wall is correspondingly diminished, but accompanying hypertrophy may tend to maintain a normal thickness. The papillary muscles tend to become tapered. Their bases are broad and originate relatively higher on the wall than in hypertrophy. Trabeculae carneae lose their prominence and their cylindrical form, and appear as broad, flat bands, partly blended into the underlying muscle. As in hypertrophy, the orifices of the valves, unless otherwise diseased, remain normal.

Hypertrophy of the right ventricle (Figure VII-19) is usually secondary to failure of the left but may occur independently. Sometimes the secondary form occurs even in the absence of failure when the left ventricle is markedly hypertrophic, perhaps because of enlargement of muscle bands that extend into the right ventricle from the left. Normally the trabeculae carneae occupy more of the lumen in the right ventricle than in the left. In hypertrophy they may form a massive net-

work extending from the free wall to the septum and obscuring the course of blood flow through the chamber. The left ventricle may undergo considerable hypertrophy without obvious dilatation, but in the right ventricle a proportional degree of hypertrophy without dilatation is infrequent. It may be that its thinner wall and pocket-like shape render it relatively less efficient in emptying itself under the conditions that induce hypertrophy.

Dilatation of the right ventricle, according to Grant (1953a), begins with attenuation and apparent lateral shift of the trabecular network. This may permit a considerable increase in capacity of the chamber with little change in external contour. With further dilatation, however, the free wall swells outward and bulges beyond its zone of attachment to the interventricular septum. As compared with its response in left ventricular dilatation, the septum undergoes relatively little change in area or thickness when the right ventricle dilates. At the apex, dilatation may be so great as to carry the free wall down to the level of the left ventricular apex, and the heart may then appear to have a double apex.

In the atria, dilatation and hypertrophy commonly occur together. Hypertrophy, with thickening of the walls and prominence of pectinate muscle, is often overshadowed by dilatation. Particularly in the left atrium, dilatation is occasionally enormous.

Rogers and Wittels (1957) have reviewed 10 cases of bilateral atrial enlargement in each of which the left atrium had a postmortem capacity of at least 1000 ml. The largest left atrium was reported to have had a volume of 3000 ml. at autopsy (Minkowski, 1904), the largest right atrium, 2150 ml. (Taussig, 1937).

Histology of Enlarged Heart. Microscopic descriptions of myocardial dilatation and hypertrophy differ widely, principally because of differences of opinion as to whether observed abnormalities are an intrinsic part of the enlargement or are manifestations of associated disease. Adopting the point of view that only alterations in the dimensions of myocardial fibers and their components are unequivocally part of the enlargement, one often finds scant evidence on ordinary microscopic

examination of the changes that were so obvious in the gross.

The acutely dilated heart may show some attenuation of fibers but, more often, no clear deviation from normal is detected. In chronic dilatation an expected thinning of fibers is concealed by accompanying hypertrophy. Changes revealed only by quantitative microscopy are described in a following section on the pathogenesis of dilatation.

In hypertrophic hearts, fibers cut longitudinally appear wider than normal, and in cross-section their diameter is increased (Figure VII-20). Whether myofibrils increase in size or number proportionately with increase in sarcoplasm is uncertain, but there is undoubtedly an increase in myofibrillar material. Nuclei may also be enlarged, and rather commonly change from an oval to a rectangular outline in longitudinal section (Figure VII-13). German authors in particular (*e.g.*, Linzbach, 1947, Nieth, 1949, Henschel, 1952) stress that, with increasing hypertrophy, there is a great increase in nuclei having horseshoe, staghorn or dumbbell shapes, eccentrically lo-

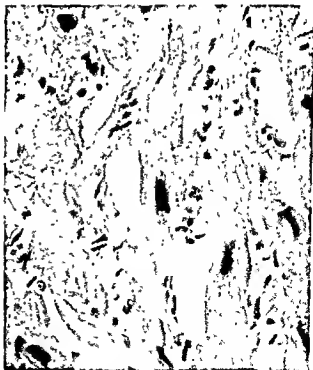


Figure VII-20. Section from a hypertrophic left ventricle to illustrate enlargement of the myofibers and the large dark nuclei with square ends. Compare with the atrophic myocardial fibers shown in Figure VII-15. Hematoxylin and eosin. X 240.

cated, doubled nuclei, groups of small nuclei set close together in a row, and nuclei with deep longitudinal grooves. Except for grooved nuclei, these ordinarily rare forms are thought to be indicative of amitotic division, that is, of myocardial hyperplasia.

In addition, a number of frankly degenerative changes have been described in myocardial hypertrophy. They consist of swelling of sarcoplasm with consequent disproportion in relative amount of sarcoplasm and of myofibrils, vacuolization, increased pigment adjacent to nuclear poles, basophilic and fatty degeneration, and coagulation and clumping of myofibrils. Even minute but widespread foci of necrosis accompanied by inflammation and followed by fibrosis have been attributed to hypertrophy (Linzbach, Nieth). These are changes recognized as commonly associated with myocardial hypoxia. The case for considering them a manifestation of hypertrophy rests on assumptions that the blood supply to hypertrophic fibers is deficient and that the decrease in surface area, relative to volume in an enlarged fiber, is unfavorable to its metabolism. The more frequent occurrence of degenerative changes in the higher grades of hypertrophy is regarded as supporting this view. However, in order to establish hypertrophic muscle as inherently subject to hypoxia, other causes of hypoxia (particularly disease of the coronary arteries) must be excluded.

Pathogenesis of Dilatation. Cardiac dilatation may develop almost instantaneously in certain arrhythmias, trauma, valvular rupture, pulmonary embolism, or myocardial infarction. It may appear in a few days or weeks in some instances of myocardial infarction or in acute myocarditis, acute anemia, poisoning, and severe infections. It may progress slowly for years, or increase acutely, in the course of chronic disorders. Most commonly, dilatation results from hypertension, coronary atherosclerosis, and valvular disease, these being the commonest causes of heart disease. If the underlying disorder is corrected, dilatation may subside completely or in part (Kerr, 1957). Persistent dilatation results either from persistence of the underlying dis-

ease or from permanent changes in the structure of the myocardium.

Elongation of myocardial fibers has long been assumed to be responsible for dilatation, but actual demonstration of a lengthening of fibers has only recently been reported. Hort (1957) prevented the usual postmortem contraction of the hearts of guinea pigs in which he had induced right ventricular dilatation and, after fixation, measured the area of the ventricular wall and the distance between Z-bands in the ventricular fibers. The interband distance proved to vary directly with the square root of the ventricular area, and he concluded that the dilatation could be wholly accounted for by lengthening of muscle fibers. He then showed that the dilatation and associated elongation of fibers were reversible; these he regarded as qualitatively similar to the changes occurring normally during the cardiac cycle. He believed that he had thus demonstrated the anatomic basis of Starling's law of the heart. By counting myocardial fibers along a line through the wall of the heart, Hort showed also that in the acutely and reversibly dilated heart, the elongation of fibers was accompanied by a reversible shift in the position of the fibers relative to one another. The thinned fibers thereby maintained the continuity of the myocardial fabric as it expanded to enclose an increased volume of blood. Mechanisms by which such a reversible shift might occur have been suggested by von Hayek (1939), C. Weitz (1951), and W. Weitz (1952) as well as by Hort.

The existence of a second important component of cardiac dilatation, irreversible and unrelated to elongation of myocardial fibers, has been advocated by Linzbach and his associates. Linzbach and Linzbach (1951) fixed in formalin human hearts removed routinely at autopsy, covering a wide range of size, weight, and age, and measured the distance between Z-bands in unstained frozen sections by phase microscopy. They found unexpectedly that the interband distance varied little from one specimen to another and that such variations as occurred were unrelated to the presence or absence of dilatation. It seemed that in all of the fixed hearts, irrespective of their gross appearance, the myocardial fibers were in nearly the same state of contraction. Subsequently, Linzbach (1956) measured the length of nuclei and the internuclear distance along myocardial fibers. The measurements showed regular variations only with ventricular weight. Again, there was no correlation with dilatation. It ap-

peared, therefore, that dilatation as it is commonly observed in the fixed human heart is the result neither of stretching nor of disproportionate longitudinal growth of myocardial fibers.

Linzbach believed that the dilatation he studied was the result of a weakening or destruction of the connective tissue binding myocardial fibers to one another, brought about by inflammation or hypoxia. Under the stress of systolic tension, the myocardial fibers in affected foci gave way to new positions where they eventually became fixed once more, forming a myocardial wall permanently thinner than before and enclosing a greater volume of blood. The changes he envisioned were like those in the formation of a cardiac aneurysm, except that they occurred in many small foci and at different times. Linzbach called this component of cardiac enlargement "structural dilatation."

If the relative magnitude of the two components of dilatation just described is indicated by comparisons of cardiac size before and after death, such as those of Friedmann (1951) previously described, it appears that the irreversible component might frequently be large. In the dynamics of the diseased heart, the role of this component would differ importantly from the reversible component dependent upon elongation of fibers (e.g., in respect to Starling's law). Hence, if the validity of Linzbach's concept of structural dilatation is established, present interpretations of the functional significance of cardiac enlargement may require much revision. If such validity is established, some of the present difficulties in understanding cardiac function in the diseased heart may be resolved. On the other hand, observations made in normal persons or in short-term experiments in animals may find a more limited application to the study of disease in the chronically enlarged heart.

CAUSES OF HYPERTROPHY

Numerous causes of cardiac hypertrophy have been recognized. The more important are briefly discussed.

Among causes of hypertrophy in the left ventricle are arterial hypertension, aortic stenosis or regurgitation, interventricular septal defect, rarely chronic adhesive pericarditis, and questionably chronic physical overexertion. In the right ventricle, hypertrophy is usually secondary to left ventricular failure, but it also occurs in mitral stenosis, septal de-

fects, and patent ductus arteriosus, and in tricuspid disease, chronic anemia, pulmonic regurgitation, and thyrotoxicosis. Both ventricles may be involved in so-called idiopathic hypertrophy of infancy and childhood.

In the atria, hypertrophy is usually caused either by failure of the corresponding ventricle or by disease of the atrioventricular valve.

The left ventricle is capable of undergoing greater hypertrophy than the other chambers. In it the greatest hypertrophy results from aortic valvular disease, particularly stenosis, and from long-standing systemic hypertension. Lowe and Bate (1948b) encountered a heart weighing 2350 Gm. in a young man who dropped dead while dancing. It showed aortic stenosis and microscopic evidence of rheumatic myocarditis and syphilitic aortitis.

Coronary Atherosclerosis. Coronary atherosclerosis may cause left ventricular hypertrophy of mild or moderate degree (see page 580). Contrary opinion is usually based on the possibility that unrecognized systemic hypertension may be responsible for hypertrophy attributed to coronary disease. The frequent association of the two conditions is unquestioned.

Clawson (1939) found, for example, that 45 per cent of 928 patients showing coronary atherosclerosis at autopsy had had hypertension. Nevertheless, Friedman (1951) found an abnormally great myocardial volume in 9 of 19 patients with coronary atherosclerosis who had not been hypertensive and Connolly and Littman (1951) found hypertrophy, defined as a ratio of heart weight to body weight greater than 0.5 per cent, in 28 of 30 patients without hypertension in whom marked coronary atherosclerosis was found at autopsy. The latter found hypertrophy in all of 21 patients with both coronary disease and hypertension. In these patients, weight of the heart averaged one-third greater than in the patients with coronary disease alone. Jezer and associates (1953) concluded from a review of 8500 autopsy protocols that coronary atherosclerosis is not a cause of hypertrophy, but their rejection of all cases showing nephrosclerosis may have biased their results. Jones (1953) noted that in hypertensive patients hypertrophy was less pronounced in instances where autopsy disclosed severe cor-

nary atherosclerosis. He was uncertain whether myocardial ischemia caused by the coronary disease prevented full development of hypertrophy, caused it to regress, or halted it by bringing about early death, but he regarded his observations as inconsistent with the view that hypoxia induced by coronary insufficiency is a cause of hypertrophy.

Myocardial infarction is recognized as a cause of hypertrophy (Karsner, 1955, page 414). Busch (1953) reported 4 cases of massive infarction in which hypertrophy of the residual myocardium occurred in the free wall of the ventricle but not in the septum. He thought that this represented a special form of myocardial enlargement and called it "vicarious hypertrophy."

Systemic Arterial Hypertension. Systemic hypertension is the commonest cause of left ventricular hypertrophy and, except for aortic valvular disease, is responsible for the greatest degree of hypertrophy. Jones (1953) weighed the free walls of the ventricles in 130 instances of hypertension and found that, in general, left ventricular hypertrophy was greater with greater mean elevation of blood pressure. Hypertrophy seemed to progress even after the onset of heart failure. In cases of long standing, slight hypertrophy of the right ventricle may also occur, even in the absence of failure. With failure, right ventricular hypertrophy may be pronounced and, according to Jones, is roughly proportional to the duration of failure.

Clinically, hypertension may persist for long periods without causing detectable enlargement. Kleinfeld and Redish (1952) reported 45 cases in which diastolic blood pressure had been above 90 mm. for 5 to 20 years and in which satisfactory height-weight data and repeated roentgenograms of the heart were available. They found that the size of the heart was within normal limits in 29 of the group at the time hypertension was discovered and in 11 remained so throughout the period of observation. Of the 16 patients showing enlargement initially, no progression of enlargement was detected in 7. Five, of 14 patients in whom congestive failure occurred, had normal heart shadows both before and after failure. Size or change in size showed little correlation with either the duration or the degree of

hypertension. Although these results seem to indicate that hypertension does not regularly cause hypertrophy, it is more probable that a difference of a few millimeters in the thickness of the myocardium, which would represent a considerable difference in its weight, cannot always be detected during life. White (1951) has pointed out that, in a large man, the heart may not appear enlarged on clinical study even though it proves to weigh as much as 425 Gm., though serial roentgenograms increase the likelihood of detecting enlargement. When dilatation is also a factor, enlargement is recognized sooner, but in hypertension dilatation is often a late development. Rarely autopsy discloses no hypertrophy in patients known to have had hypertension (Gross and Jezer, 1949).

As seen at autopsy, hypertrophy caused by hypertension has no distinctive features. It is more likely, however, to be of the concentric type, i.e., without accompanying dilatation, than is the hypertrophy associated with other disorders. Slight endocardial thickening and myocardial fibrosis are commonly seen, and the latter may be increasingly prominent in the higher grades of hypertrophy. Accompanying coronary arteriosclerosis may be the principal factor in the production of these lesions.

Pulmonary Hypertension and Cor Pulmonale. Pulmonary hypertension is the commonest cause of right ventricular hypertrophy. Usually the result of left-sided heart disease, particularly mitral stenosis and left ventricular failure, pulmonary hypertension may occur also in congenital defects that divert blood under systemic pressure into the pulmonary circulation and in disease of the lungs. When disorders originating in the lung give rise to right ventricular hypertrophy, dilatation, or failure, the clinical condition is called pulmonary heart disease, or cor pulmonale.

As in the left ventricle, hypertension causes no distinctive enlargement or microscopic change in the right ventricle. Clinically, enlargement usually becomes apparent when pulmonary blood pressure is about twice normal, but owing to the form of the right ventricle, a considerable degree of hypertrophy or dilatation may occur without appreciable change in its external configuration. The right

ventricular hypertrophy is often greater in pulmonary disease, however, than in enlargement secondary to disease of the left side of the heart. It is said that if both ventricles are hypertrophic in the absence of mitral stenosis, congenital defects, or pulmonic stenosis, a right ventricular weight greater than one-half that of the left ventricle signifies some degree of pulmonary heart disease.

In recent years, improvement in diagnostic methods has increased the recognition of pulmonary heart disease; improvement in therapeutics has also increased its incidence since more patients with pulmonary disease live long enough for the heart to be affected. Functionally, the responsible pulmonary disorders are characterized as a group by their interference with exchange of gases between blood and air in the alveoli. Immediate factors are the pulmonary hypertension and such secondary influences as anoxia, increased blood volume, polycythemia, increased cardiac output, and disordered breathing mechanics (Richards, 1957). Morphologically, the lungs may show lesions suggesting a reduction in vascular bed and in alveolar tissue. Depending upon the disorder, the pulmonary lesions include diffuse emphysema, fibrosis, and chronic and acute inflammation—the last because acute respiratory infection is often the precipitating factor in fatal cardiac failure. Vascular lesions include old or recent thrombi, intimal or medial thickening of smaller vessels, and atheromatous plaques in main arterial branches.

Frequently, the correlation is poor between cardiorespiratory embarrassment observed clinically and pulmonary lesions observed postmortem. McKeown (1952) has pointed out that similar lesions may be observed both in the presence and in the absence of a history of preceding pulmonary heart disease. It is postulated that hypoxia causes vasoconstriction which in turn contributes importantly to the development of pulmonary hypertension. Clinical evidence for this effect of hypoxia consists of a rough parallelism between the degree of hypertension and the degree of hypoxia, and the tendency for pressure to fall with relief of hypoxia (Richards). It may be, therefore, that the presence or absence of vasoconstriction during life accounts for some of the discrepancies between clinical signs and morphologic observations.

The pulmonary disorders most commonly responsible for chronic hypertension and right ven-

tricular hypertrophy are chronic pulmonary emphysema, chronic bronchiectasis, bronchial asthma, pneumoconiosis, tuberculosis, and the pulmonary effects of kyphoscoliosis. Disorders less commonly reported are sickle cell anemia, schistosomiasis, sarcoidosis, scleroderma, embolism by multiple small emboli, and various fibrotic lesions of uncertain etiology. Rarely chronic cor pulmonale may develop also in a patient who survives a massive embolus in the main branch of a pulmonary artery. Cor pulmonale of necessarily shorter duration occasionally appears in a patient with diffuse pulmonary vascular spread of metastatic tumor, among which carcinoma of the stomach is noteworthy. Acute cor pulmonale is usually the result of a sizeable pulmonary embolism that is not immediately fatal.

Hypertrophy in Infancy and Childhood. In most instances, cardiac enlargement in the early years of life is the result of congenital structural defects. A number of instances of enlargement were once placed also in a category called "congenital idiopathic hypertrophy." Most of the cases formerly so classified can now be identified as examples of glycogen storage disease, idiopathic myocarditis, subendocardial sclerosis (endocardial fibroelastosis), medial necrosis of coronary arteries, or aberrant coronary artery (Roscnbaum *et al.*, 1953). The prenatal origin of some of these conditions is apparent from their nature or from their discovery shortly after birth. In some instances, similar lesions discovered later in infancy or in early childhood are assumed, therefore, also to be of congenital origin.

Idiopathic Hypertrophy in Adults. In occasional instances, cardiac enlargement occurs in later childhood and adult life in the absence of any presently recognized cause of heart disease. A greater incidence has been noted in men than in women, and in young adults than in older persons. The myocardium has been variously described as showing no change, vacuolization of fibers, focal necrosis, slight inflammation, and minute scars. Mural thrombosis has been frequently noted, together with embolization in various organs. Death usually occurs in congestive heart failure. *The clinical history has not seemed to be relevant in any instance. (See reviews of*

Norris and Pote, 1946; Serbin and Chojnacki, 1955.)

Both in children and adults, refinements in diagnosis have reduced the number of hearts that must be relegated to the category of idiopathic hypertrophy. Thomas and associates (1951), for example, reviewed 10,000 autopsies and found 24 instances in which dilatation or hypertrophy was not associated with a clearly defined entity. On reexamination 2 of these showed no distinguishing characteristics other than the enlargement, a third showed "a tremendously dilated paper-thin ventricle" without hypertrophy, similar to a remarkable case first mentioned by Osler and more recently described by Segal (1950), and a fourth showed giant-cell myocarditis. The remaining 20, from infants, children, and adults, showed endocardial fibroelastosis with or without patchy myocardial fibrosis. The authors believed that since the lesions were similar in all 20, they were probably congenital in all.

Physical Activity. The observation of cardiac hypertrophy in experimental animals after prolonged severe physical exertion suggests that hypertrophy of similar origin can occur in man. That strenuous sports or prolonged hard work causes such enlargement in healthy persons is uncertain, however. There is uncertainty, too, with respect to the effects of physical activity on cardiac size in instances of previous or concurrent heart disease and on the development of heart disease subsequent to a period of unusual exertion. The view that large hearts are necessarily diseased may be a source of bias. The basic difficulties lie in definition of the normal heart and in selection of suitable subjects for study.

Pathogenesis of Hypertrophy. In general usage, an increase in the mass of the myocardium is termed *hypertrophy*. Few enlarged hearts are now classified as examples of "idiopathic hypertrophy," but even in instances in which a given condition seems clearly to initiate hypertrophy, the precise nature of the stimulus remains in doubt and the ensuing events are largely unknown. A current theory is that hypertrophy is the result of increased myocardial work; another theory is that hypertrophy is the result of cardiac dilatation.

The "work theory" is based on the common

observations that in many conditions associated with hypertrophy the heart either performs increased work or expends increased energy to accomplish a given amount of work, and that those chambers are enlarged in which the work-load is increased. Thus, hypertrophy occurs with increased cardiac output in arterio-venous fistula; with increased resistance to circulation in hypertension; with increased filling of a chamber in valvular insufficiency or septal defect; and with increased rigidity of the cardiac wall in fibrotic lesions. Similarly, destruction or injury of myocardial fibers in myocardial infarction is followed by hypertrophy of those fibers remaining. Furthermore, when the work-load is decreased, hypertrophy may regress.

Thus, Matas and Heninger (1939) observed regression of presumed hypertrophy following removal of a cavernous hemangioma, and Shaffner and Bradshaw (1950) found that the size of myocardial fibers in dogs diminished following closure of an arterio-venous fistula which had induced hypertrophy.

A corollary of the "work theory" is that hypertrophy is compensatory in that it permits the heart to overcome handicaps imposed by disease. This view has been questioned in a provocative review by Grant (1953a). It has not been proved that hypertrophic cardiac muscle is stronger than the normal myocardium. Patients who survive a sudden great increase in cardiac work, as in rupture of a valve leaflet, show no notable improvement with the development of hypertrophy, and the few hypertensive patients who fail to develop hypertrophy seem to fare no worse than those whose hearts enlarge. Evidence that the blood supply of the heart is potentially inadequate (Roberts and Wearn, 1941) also casts doubt on the compensatory nature of hypertrophy.

The theory that dilatation is the cause of hypertrophy is based on the observation that cardiac dilatation commonly precedes hypertrophy. In human cardiac disorders of short duration, an enlargement is likely to be the result of dilatation, whereas in chronic disorders, the heart is usually hypertrophic.

A similar sequence of dilatation followed by hypertrophy has been reported in animals in which aortic stenosis or arterio-venous fistula has been produced (Eyster, 1927; Holman, 1937).

Various suggestions have been made as to how dilatation might induce hypertrophy: that the elongated fibers in a dilated heart have a greater surface area relative to their volume, thereby facilitating surface reactions and the entry of nutrients, that the requirement for increased energy which elongated fibers expend in accordance with the law of the heart stimulates hypertrophy; that stretching of the fibers is the stimulus for their enlargement, and that the stretching is actually injurious and the injury initiates hypertrophy, even if the dilatation itself should subside. The view that injury is the stimulus to hypertrophy was advocated by Eyster and his associates (1927, 1928) who produced temporary dilatation of the heart in dogs and reported vacuolization of myocardial fibers and subsequent hypertrophy. Later work, however, has not confirmed these observations (Kerr, 1957).

The most cogent objection offered to dilatation as the cause of hypertrophy in man is that hypertrophy may occur without evidence of preceding or accompanying dilatation. Particularly in hypertensive patients without congestive failure, there may be no clinical evidence of dilatation, and autopsy may show only hypertrophy. At present it appears that both dilatation and hypertrophy are responses to cardiac stress, mediated in an unknown fashion, and that dilatation is commonly the earlier and more rapid; and that a causal relationship between the two responses has not been established.

Hyperplasia of Myocardium. There is no doubt that individual myocardial fibers are enlarged in cardiac hypertrophy. There is a strong possibility that an increase in the number of myocardial fibers also may contribute to an increase in myocardial mass, but neither qualitative nor quantitative evidence presently available is conclusive. Mitosis of myocardial nuclei has rarely been observed after early infancy and has not necessarily been associated with cardiac hypertrophy (Herzog, 1924; MacMahon, 1937; King, 1940). If hyperplasia occurs, therefore, it must be presumed to be associated with amitotic nuclear division, but qualitative nuclear changes (described under Histology of Enlarged Heart, page 537), suggestive of such division, are not unequivocal. Division of the fibers has been

thought to occur through longitudinal splitting, which may begin at points of anastomosis, but histologic evidence of this process is not clear-cut. Quantitative changes indicative of myocardial hyperplasia are described below, but such changes, revealed by enumeration or measurement of myocardial fibers, have necessarily been observed only in small myocardial samples which may not have been representative of the hearts from which they were obtained. Furthermore, the approach to quantitative investigations has been based on the belief that cardiac muscle is a syncytium of anastomosing fibers without division into separate cells and hence without measurable length. As a result, it has been necessary to make assumptions as to one or more dimensions of cardiac fibers which may not be justifiable. The studies of Sjöstrand and Anderson (1954) with the electron microscope indicate that the intercalated disks represent cell boundaries in cardiac muscle.

Karsner and associates (1925) compared a normal heart weighing 300 Gm. and a hypertrophic heart weighing 500 Gm. with respect to breadth and number of fibers in microscopic sections of known area and depth. They found that the average breadth of fibers in the heavier heart exceeded that of fibers in the smaller heart in nearly the same proportion that the weight of the heavier heart exceeded that of the smaller. By assuming that myocardial fibers were rectangular structures of which the length and thickness were defined by the length and depth of the microscopic sections, Karsner and his associates were able to calculate the total fiber content of the 2 hearts from the known volume of the microscopic sections and the average number of fibers per section. The two totals differed by only about 5 per cent. The results indicated, therefore, that there had been no appreciable multiplication of fibers in the hypertrophic heart and that an increase in the breadth of existing myocardial fibers accounted for the hypertrophy.

In a similar study, Lowe and Bate (1948a) compared two hypertrophic hearts weighing 567 Gm. and 850 Gm. They found that although the fibers were wider than normal, the average width was the same in the 2 hearts despite the difference of nearly 300 Gm. in their weight. They suggested that the larger heart might have had a higher content of water or of connective tissue.

In a subsequent study of a heart weighing 2380 Gm., Lowe and Bate (1948b) concluded that the myocardial fibers were far too narrow to account for the weight of the heart if it were assumed that it contained the same number of fibers as a normal heart. Histologically, many fibers appeared to have split lengthwise and pairs of closely juxtaposed nuclei were numerous. The authors concluded that hyperplasia of myocardial fibers must have occurred.

In 1947, Linzbach developed an equation for predicting the size of myocardial fibers relative to myocardial weight, and he and his colleague, Henschel, applied the equation to massive data on enumeration and measurement obtained from fibers of hearts weighing 45 to 1120 Gm. They reached the conclusion that beyond early childhood, all normal and moderately hypertrophic hearts contain the same number of fibers and the length of the fibers varies proportionately with their diameter, but that in higher grades of hypertrophy (above a weight of 450 to 500 Gm.) multiplication of fibers occurs in some hearts (Linzbach, 1947, 1950, Henschel, 1952). The results of an enumeration of myocardial nuclei were consistent with these conclusions. In addition, Henschel found that the incidence of double nuclei was significantly greater than normal in hearts that were hyperplastic according to Linzbach's equation.

There appears to be no significant disagreement in the data of the three investigations just described. Linzbach and Henschel found no evidence of appreciable hyperplasia in hearts weighing 500 Gm. or less, and in this respect their results agree with those of Karsner and associates. In hearts weighing more than 500 Gm., Linzbach and Henschel did find evidence of hyper-

plasia and here their observations agree with those of Lowe and Bate.

With respect to the functional significance of myocardial hyperplasia in cardiac hypertrophy, it might be supposed that the splitting of fibers would facilitate exchange of materials between fibers and capillaries. The exchange might be supposed to be further improved should capillary hyperplasia also occur. Roberts and Wearn (1911) found a capillary-fiber ratio of 1:1 in hearts of widely varying weight. Hort (1955) confirmed this observation in hearts which were hyperplastic according to Linzbach's equation. He concluded that, on a capillary level, hyperplasia of the myocardium is associated with an anatomically improved blood supply.

The evidence with respect to hyperplasia of myocardial fibers and of capillaries, together with the results of histologic examination, has led Linzbach to regard a cardiac weight of 500 Gm. as a "critical weight." He believes that in hearts exceeding this weight, either the heart became hyperplastic and thus able to remain for a time in a good functional state despite continued increase in mass, or the myocardium developed progressively severe hypoxic lesions with consequent cardiac dilatation and failure. *According to this concept, it is only with the onset of hyperplastic or hypoxic changes that cardiac hypertrophy can be regarded as truly pathologic.*

THE EFFECT OF AGING ON THE HEART

It is difficult to separate the tissue changes produced by aging from the pathologic monuments of diseases which may have been present earlier in life. One cannot easily escape the conviction that in this field we are employing methods similar to those of the archeologist and that much of the evidence is necessarily circumstantial. It is not justifiable to attribute the lesions found at autopsy in old people to age alone, unless the effects of previous disease can be excluded with certainty. This is a point which many authors

overlook. What is needed is not only a careful study of persons dying accidentally, but also a critical clinical and pathologic study extending over the entire lifetime of selected groups of individuals. Obviously this would be a difficult undertaking.

Karsner's paper (1940) on the subject is the most critical and his remarks are worth quoting:

"The pathologist rarely sees an autopsy upon a person dead of old age. In 400 autopsies upon persons over 65 years of age, Aschoff found no deaths attributable solely to old age (marasmus

senilis, 'Altersschwache'). . . . We have no record of it in more than 19,000 autopsies on people of all ages. . . . The changes often attributed to involution may be, in part at least, the sequels of disease long past.

"There have been various studies of the effects of aging upon the heart. Mönckeberg quoted French authors to the effect that it is enlarged. Duthoit, Warembourg and Pinchart stated that this is true roentgenologically. W. Muller is said to have found that the highest average weight of the heart is in the seventh decade. It is probable, however, as Monckeberg suggested, that these studies have failed to take into account the effects of hypertension. Aschoff, as the result of his observations, stated that the weight of the heart does not vary significantly from the normal. Kirch described a reduction in the size of the heart especially in its infrapapillary or apical portion. Aschoff agreed that this is true, but attributed it to reduction of coronary blood supply, rather than the effect simply of involution. Kirch distinguished between the gross appearance of senile atrophy and 'cachectic' atrophy, but the differences are not significant. Monckeberg, in particular, drew attention to the similarities of so-called senile atrophy and that which is a part of the general atrophy observed in nutritional edema. The conduction system does not share in the atrophy. It has been said that the heart weight: body ratio is reduced. In old age, however, the weight of the body is often altered by atrophy of skeletal muscle, of fat and bone, so that the ratio is not altogether dependable. Kirch stated that the atria and the four valvular ostia are enlarged, and also that the mitral leaflets bulge toward the atrium in umbrella-like fashion, especially between the attachments of the chordae tendineae.

"This last change is occasionally found in persons of earlier life, when it is interpreted as due to disease and usually a disease that can be recognized, the same disease may have lost its identifying features in the aged. Thus can also be said of increased depth of the sinuses of Val-salva and enlargement of the corpora arantii. Karsner and Koletsky and others have found that calcific sclerosis of the aortic valve is almost always due to inflammatory lesions especially those of rheumatic fever, rather than to aging. Gross thought that coronary anastomosis increases with age, but Blumgart, Schlesinger and Davis related this change to disease rather than to age.

"Microscopic examination yields little, if any, further information. What has been said above about atrophy is equally applicable here. It is said that the pigment in the fiber cells increases with age. Monckeberg quoted Lubarsch as having seen out-spoken brown atrophy in patients dead of inanition at from 25 to 39 years, and Prym as finding no real difference in this respect between the condition in old age as compared with inanition. There is no convincing evidence that this Abnutzungspigment is due to wear and tear or to disease. It is, however, a combination of lipid and pigment and is introduced in part at least in food, and the longer a man lives the more he may absorb.

"Miller and Perkins reported, on the basis of histological methods, that the heart of the aged shows an increase of elastica, but their method and the small number of observations do not provide convincing evidence. Aschoff quoted Rondolini as having found an increase of elastica in the nodes of the conduction system, but this also requires confirmation."

CARDIAC FAILURE

The pathologic physiology of the condition and its manifestations in other organs or tissues are discussed in Chapter V.

The commonest conditions in which congestive failure occurs are valvular defects, particularly of the mitral and aortic valves, chronic arterial hypertension, and myocardial infarction following coronary occlusion. Less common but important are severe rheumatic carditis, thyrotoxicosis, chronic pulmonary disease, congenital defects, anemia, and prolonged tachycardia. Infrequent or rare causes are arteriovenous aneu-

rysm, cardiac trauma, thoracic deformities, external pericardial adhesions, tumors, and malnutrition (White, 1951). The onset of congestive failure is frequently precipitated by a complicating condition which either injures the heart directly or increases its work-load. The commonest precipitating factor is infection, such as respiratory infection, which may either involve the heart directly as in myocarditis or endocarditis, or indirectly. Other precipitating factors are reduced coronary blood flow from any cause, changes in cardiac rate and rhythm, pregnancy and childbirth, hemorrhage, anemia, transfusions

and infusions, pulmonary embolism, and physical and emotional stress.

At autopsy of patients who have died of congestive failure, enlargement of the heart is an almost constant finding. Dilatation is the rule and hypertrophy may be present if heart disease is of more than a few weeks' duration. Neither the size of the heart nor any other morphologic feature is specific evidence of failure; the same lesions may be seen in hearts which have not failed.

Failure of the heart may also occur in the absence of the congestive syndrome. Such failure

is abrupt in onset and short in duration, and its effects are principally those of inadequate blood supply to such vital structures as the brain and the heart itself. If the patient survives, he may develop congestive failure. Autopsy in instances of acute failure may show dilatation of the right ventricle but there are no changes that can be regarded as diagnostic. A common cause of acute failure is sudden alteration in rhythm. Other causes include acute cardiac injury, as in myocardial infarction, diphtheritic necrosis or rupture of a valve, and sudden mechanical hindrance to cardiac output, as in cardiac tamponade, massive pulmonary embolism, and obstruction of a valve orifice by a thrombus.

CARDIAC CHANGES IN SHOCK

In dogs it has been shown that shock may cause focal loss of striations, eosinophilia of the cytoplasm and pyknosis of the nuclei of myocardial fibers within 24 hours. After 2 to 7 days, gross lesions appear which are scattered, yellow or gray and occur most often

beneath the endocardium. In these areas certain fibers are necrotic and others show fatty changes. Usually an acute inflammatory exudate is also present. Burdette (1951) has demonstrated profound changes in the metabolism of the cardiac muscle.

EFFUSIONS IN PERICARDIAL SAC

Hydropericardium. The pericardial sac normally contains clear, watery, pale yellow fluid having a low concentration of protein and a low specific gravity. When the fluid exceeds 100 ml., the condition is known as hydropericardium. Such fluid transudate is to be distinguished from serous or other exudate occurring in pericarditis.

As part of a general tendency to accumulation of fluid in tissues and serous cavities, hydropericardium occurs most commonly in congestive heart failure. It is also seen, however, in subacute glomerulonephritis, nephrosis, myxedema, and beriberi. Perhaps as a manifestation of nutritional hypoproteinemia, excessive pericardial fluid may occur late in the course of wasting diseases. Local impairment of venous flow may result in hydropericardium, as when mediastinal tumors or inflammations compress or obstruct the veins draining the pericardium.

The effects of hydropericardium depend upon the amount of fluid and particularly upon the speed with which it develops. The normal pericardial sac is capable of expand-

ing to hold a liter or more of fluid without exerting a serious compressive effect on the heart or on the veins entering the heart, provided the accumulation is slow. But if the accumulation is rapid, a few hundred milliliters may exert severe or fatal compression (cardiac tamponade) by restricting the filling of cardiac chambers and diminishing venous flow within the sac. If the parietal pericardium is already thickened by disease, compressive effects will be produced by slower or smaller accumulations of fluid.

Hemopericardium. The escape of unmixed blood into the pericardial sac has effects similar to those of hydropericardium, but since hemorrhage is likely to be both faster and more abundant, cardiac tamponade is more likely to occur. Causes of hemopericardium include direct trauma, rupture of pericardial vessels, rupture of the heart, and rupture of the intrapericardial portions of great vessels. Minor hemorrhages may occur in metastatic tumor of the pericardium or as part of an inflammatory exudate.

Pneumopericardium. Air may enter the pericardial sac and occasionally may cause cardiac compression. The usual means of entry is through traumatic perforation of the parietal pericardium. In the event of such perforation, the presence of air is likely to be obscured by other effects of the trauma. Air

may also be introduced into the pericardial sac, intentionally or by accident, in the course of therapeutic procedures. Perforation of a neighboring air-containing organ into the pericardial sac has also been reported (Harp and Peeke, 1949).

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Diseases of the Coronary Arteries

A. Atherosclerosis

S. E. GOULD*

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MORE PEOPLE die from coronary atherosclerosis than from any other disease. As man's life-span lengthens, the relative incidence of disability and the death rate from this cause continue to increase. It is en-

couraging, therefore, to note that increasing study is being devoted to the causes, treatment and prevention of coronary disease.

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Galen (138-201 A.D.) first applied the name *coronary* to the larger arteries of the heart which externally partially ring the base of the ventricles, somewhat like a crown (corona). Lobstein (1833) coined the term "arteriosclerosis."

The first correct diagnosis of coronary thrombosis made during life and verified at autopsy was reported by Hammer in 1878. His patient collapsed after an illness of 24 hours. Autopsy

disclosed closure of the ostium of the right coronary artery by thrombotic masses which had their origin from the right aortic cusp (embolic bacterial vegetations). Dock (1896), Obrastzow and Straschesko (1910) and Hochhaus (1911) also reported instances of coronary occlusion recognized during life; but the classic description of clinical "coronary thrombosis" with substantiation at autopsy was published by Herrick in 1912 (see historical account, page 13).

CORONARY ARTERIES

Anatomy of the Coronary Arteries. The coronary arteries are arteries of the fourth order, their caliber corresponding to that of the distal portion of the radial arteries. For the gross anatomy of the coronary arteries, see Chapter III, page 103. The coronary arteries are of muscular type (Wolkoff, 1929; Benninghoff, 1930), showing a sudden transition from the aorta which is an elastic artery. After infancy, the intima contains a subendothelial layer of connective tissue, next to which is a prominent elastic-hyperplastic layer and external to the latter, a musculo-elastic layer. The media is composed of circularly-disposed muscular fibers which are accompanied by elastic fibers. The elastic fibers are delicate in the inner half of the media and coarse in the outer half. No distinct elastica externa is present. The adventitia is composed of collagenous and elastic fibers and is not well developed. The coronary arteries are richly supplied with vasa vasorum. The coronaries, thus, are characterized by the thickness of the intima, a well-developed muscular media and a thin adventitial layer. The increase in intimal thickening affects particularly the first portion of the coronary arteries, the first portion of the main branches of the left coronary, and the main branches at the sites of origin of secondary branches. In comparing the main stems of the two coronary arteries, the left artery has an intimal connective tissue layer that is less well developed than the right artery, and elastic-hyperplastic and elastic muscular layers that are better developed, while its media contains relatively more and

coarser elastic fibers (Benninghoff). It is believed that in the development of atherosclerosis, the initial deposit of lipoid material takes place primarily in the elastic-hyperplastic layer. This change is succeeded by connective tissue proliferation, formation of collagen or hyaline connective tissue, and calcification.

Difference, in Sexes, in Coronary Arteries of Newborn. Dock (1946) studied sections of the main coronary arteries of 12 newborn infants of each sex. He found that, on the average, the thickness of the intima in males was 26 per cent of that of the entire vessel, while in females it was but 8 per cent. He concluded that this difference in structure serves to explain the sex difference in incidence of coronary occlusion in later years of life.

His findings were confirmed by Fangman and Hellwig (1947) and Minkowski (1947). Wdems (1951) also suggested that the diffuse overgrowth of intimal tissue which occurs early in life is related to the same mechanism that eventually leads to formation of atherosclerotic plaques, chiefly because both changes commonly develop at the same sites of affected arteries. Schomagel (1956) studied sections of the first 2 cm. of the ramus interventricularis anterior. In 28 newborn infants up to 24 hours old, he obtained some confirmation of Dock's findings. In 60 infants ranging from 1 day to 1 year of age, however, he found no significant difference in thickness of the intima in the two sexes.

Thus, it is currently believed that in the newborn, particularly in the male, the changes in the intima, represent the earliest stages of atherosclerosis.

Changes in Coronary Arteries Attributable to Age. Moon (1957) could demonstrate no lesions of the coronary arteries in fetuses 3½ to 9 months of age. In newborn infants he observed rupture and fragmentation of the internal elastic layer, associated with deposition of acid mucopolysaccharide, fibroblastic proliferation, and occasionally endothelial proliferation. These processes often recurred and were followed by regeneration of the internal elastic layer.

The principal change in the coronary arteries attributable to age is a *thickening of the intima* (Wolkoff, 1929). The thickness of the intima of the coronary arteries exceeds

that of other muscular arteries and is related to the special mechanical factors, such as pressure and tension, to which the coronary arteries are subjected. At birth, the intimal layer is relatively thin and consists of a single well formed layer of elastic fibers (*lamella elastica interna*) which is covered by a layer of flat endothelium. In childhood, the thickness of the intima is about equal to that of the media; during the third and fourth decades, intimal thickness becomes maximal; in middle age and in old age, the intima is several times as thick as the media (Figure VIII-1). This thickening chiefly involves the first portions of the main vessels and the sites of



Figure VIII-1. Sections of main coronary artery from patients of different ages, to show relative thickness of intima. A, 1 month, B, 9 months, C, 14 years, D, 35 years, E, 49 years. All figures, X 100. Elastic-van Gieson.



Figure VIII-2. Heart and aorta of man of 94, showing dilatation of aorta with but minimal atherosclerosis. (WCGH, 49 A 453)

these vessels from which branches arise. It may begin to appear at birth or within a few months after birth. The thickening is brought about (1) by splitting of the internal elastic lamina from the internal limiting lamella, with the formation of a *musculoelastic layer*; (2) by splitting of the internal limiting lamella with formation of a prominent *elastic-hyperplastic layer*; and (3) by formation, in most cases, on the inner aspect of this hyperplastic layer, of a *layer of connective tissue*.

Bork (1926) observed splitting of the elastic layer of the intima in the youngest patient he examined, age 1 month, he recognized the musculo-elastic layer as early as the sixth month of life and found the connective tissue layer to be well developed at age 15. Wolkoff (1929) found that after the fifteenth year the subendothelial connective tissue becomes thicker, and within it there develops a longitudinal layer of smooth muscle. These changes in the intima, which are fully developed at 30 years of age, occur earlier and more prominently in the left coronary than in the right. With increasing age, the intima develops nodular thickenings, the media becomes narrower, the adventitia thicker.

Gross and associates (1934) found atherosclerotic changes occurring chronologically in the following order: left anterior descending branch, left circumflex, right circumflex, and posterior descending. They also demonstrated changes in the intramural arteries which are related to age and to location within the heart. These changes, which they called *fibroclastic metamorphosis*, consisted of elastification of the media, elastic-hyperplastic changes in the intima, fusion of these two layers, atrophy of smooth muscle fibers and development of irregular patches of connective tissue. With respect to time and frequency of appearance, these changes occurred earliest and oftenest at the following sites, in decreasing order: posterior papillary muscle of the left ventricle, interventricular septum, left ventricle, pulmonary conus, and atria.

The most important change caused by aging of the arterial wall in the larger arteries is a gradual *diffuse distention* (Ophuls, 1933a). This results from progressive deterioration of the elastic tissue and is not accompanied by any characteristic histologic change. Thus, in the prime of life, the circumference of the aorta at its root generally measures about 50 mm., but this increases to 70 or 80 mm. or more with advancing age (Aschoff, 1933a). The stretching of the wall occurs in a transverse as well as in a longitudinal direction and, as a result, the aorta becomes wider and longer and assumes a tortuous course (Figure VIII-2). The tortuosity of the coronaries may be accentuated by atrophy of the myocardium in old age and in wasting diseases.

Aside from this dilatation, the *walls* of the arteries *increase in thickness*, so that throughout life there is a constant increase in the total diameter of the coronaries as well as in the diameter of their lumina (Ehrlich *et al.*, 1931). Microscopically, the media shows a constant increase in number and thickness of elastic fibers, and in number of nuclei. These changes are progressive during succeeding decades, but are greatest in the first two decades during the period of greatest growth of the arteries and of the heart. During this same period of growth, the intima shows its greatest growth in the musculoelastic layer; thereafter, the hyperplastic layer develops

progressively until the end of life, probably in response to mechanical factors. During the average span of life, the cross-sectional area of arteries increases 6 to 7 times and the number of macroscopically visible arteries is doubled, the small branches increasing by approximately 80 per cent. The number of vessels distributed to the pericardial fat also increases with age.

The observations of Lansing (1954) on human material indicate that *degeneration of the elastic tissue* in the media of arteries is accompanied by calcification of the elastic tissue, is associated with age, and may occur without atheromata; and that when the two lesions co-exist, the cholesterol accumulates in the intima after the elastic tissue in the underlying media has broken down. Lansing leaves open the question of the relation between the elastic-tissue breakdown and the atheromata, and the possibility of a common factor being responsible for the production of both lesions.

Aging of Myocardium. Cohn (1939) listed a tendency of the heart to undergo the following changes with advancing age: increasing deposition of subepicardial fat along grooves of the coronary vessels, opacification of the pericardium especially over the base of the right ventricle, loss of softness and pliability of the valves (especially the aortic and mitral valves), and fibrous thickening of the left atrium and of the apices of the papillary muscles. Dock (1945) applied the term *presbycardia* to indicate myocardial senescence or that age has impaired the function of the heart even though there is no significant structural change. He believes that, in older persons without coronary atherosclerosis, this condition is often the basis for heart failure. Likewise, Harrison and Resnick (1950) stated that clinically the term *arteriosclerotic heart disease* should be restricted to patients having angina pectoris or evidence of myocardial infarction and should not be applied to elderly persons suffering from heart disease and congestive failure without obvious cause. They believe that the aging myocardium undergoes involutionary changes for which there is no recognized histologic basis and

no known clinical defect; that these involutionary changes may lead to heart failure; and that this condition should be designated *senile heart disease*. This subject is in need of investigation.

Blood Supply to the Heart. The distribution of the coronary arteries is described in Chapter III (see page 110). According to Ebrich, de la Chapelle and Cohn (1931), the right coronary artery supplies the upper two-thirds of the ventral, the lateral and dorsal walls of the *right ventricle*, and the cephalic half of the mesial aspect of the dorsal surface of the *left ventricle*; the left coronary artery supplies the greater portion of the left ventricle (except for the cephalic half of the mesial aspect of the dorsal surface), the lower third of the ventral surface of the right ventricle and that portion which borders on the sulcus longitudinalis.

The ventral two-thirds of the *interventricular septum* and generally its apex are supplied by branches of the anterior descending *ramus* (*ramus interventricularis anterior*) of the left coronary, while its dorsal third, except for the apex, is nourished by branches of the right coronary (Spalteholz, 1924).

According to Amenomiya (1910), the left anterior *papillary muscle* receives its blood supply



Figure VIII-3. Roentgenogram of ventral view of injected human heart in fourth decade. (From *The Blood Supply to the Heart* by Gross, 1921. Courtesy of Paul B. Hoehner.)



Figure VIII-4. Roentgenogram of injected heart showing distribution and direction of deeper divisions of coronary arteries (From Gross. Courtesy of Paul B Haecher.)

only from a large branch of the anterior descending ramus, while the left posterior papillary muscle receives blood from branches of both coronaries; the large lateral papillary muscle of the right ventricle is supplied by both coronaries while the medial papillary bundle is supplied only by the right coronary. In most cases the posterior papillary muscle of the right ventricle is supplied by the right coronary and, at least in part, by the left artery also (Spalteholz, 1924). Spalteholz demonstrated in the papillary muscles at least two, and usually many, anastomosing arterial branches.

In general, the *right atrium* is nourished by branches of the right coronary artery and the *left atrium* by branches from the circumflex branch of the left coronary artery. The *sino-atrial node* is supplied by a branch of the right coronary artery in 60 per cent of cases and from the left, in 40 per cent (Cross, 1921). The right coronary also supplies the *atrioventricular node*, the *main bundle* and in most cases the dorsal branches of the *left bundle*. The *right bundle* receives its blood supply from the left coronary artery. The branches of the right bundle are ordinarily

supplied by both coronaries. In cases in which the posterior descending artery (ramus interventricularis posterior) arises from the left coronary (8 per cent of hearts), only this vessel supplies branches of the right bundle.

Types of blood vessels. Functionally, the coronary arteries are end-arteries (Robb and Robb, 1912) but anatomically, in normal hearts, they possess anastomotic channels of less than 40 micra in diameter (Blumgart *et al.*, 1910). In addition to such anastomoses, other communications include veins, arteriosinusoids, arterioluminal vessels and thebesian veins, all of which communicate freely with capillaries (Wearn, 1941). (See Figure III-18.)

Importance of luminal vessels. Much of our knowledge of the anatomy of these vessels has been acquired by the injection methods of Gross (1921, Figures VIII-3 and VIII-4), Spalteholz (1921) and Schlesinger (1938, 1940). Crainicianu (1922) showed that the aggregate diameter of the luminal vessels was nearly equal to that of the coronary arteries. The arteriosinusoidal vessels are numerous and their structure, except for irregularity of the lumen, is identical with that of the capillaries (Wearn). The relative importance of the luminal channels is indicated by Wearn who found, in perfusion of the coronary arteries, that 70 to 80 per cent of the perfusate escaped directly into the heart chambers and only 20 to 30 per cent returned by way of the coronary veins. As a result of his injection studies, Schlesinger (1940) classified the distribution of the coronary arteries into three distinctive anatomic and functional patterns (see page 110).

Cardiac capillaries continually utilized. The blood flow in the capillaries of the skeletal muscle, renal glomeruli and the skin is intermittent. The work of Wearn (1941) indicates that the heart, however, utilizes all of its capillaries at all times and that the blood flow through the coronary capillaries is not intermittent. The percentage of oxygen saturation of coronary venous blood in the normal heart (of the dog) at rest is considerably lower than that of venous blood of skeletal muscle; in other words, the normal heart makes almost complete use of its available oxygen, and any increase in work of the heart must be met by an increase in the coronary flow.

Number and concentration of capillaries. According to Wearn, the number of capillaries per square millimeter in the human heart is approximately 4000 at birth, and ranges from 3000 to 4000 (mean 3342 ± 36) in adults. At birth there is 1 capillary for each 5 myocardial fibers; in the adult heart the ratio of capillaries to muscle fibers is approximately 1:1. This capillary concentration remains fairly constant throughout adult life, as does the diameter of the muscle fibers in normal adult hearts (mean diameter, 14 micra). Hypertrophy of the heart does not result in any increase in the number of muscle fibers or capillaries, but the increased size of the fibers means that there is a proportional decrease in concentration of capillaries per unit area of muscle. Physiologically, however, it does not seem that the hypertrophied heart is supplied with insufficient blood.

Dock (1941) perfused human hearts post-mortem with kerosene and noted that the *coronary flow* is decreased in *hypertrophied hearts* but found no evidence that the hypertrophied heart has an inadequate blood supply or that its fibers are too thick for adequate oxygen diffusion. In addition, the work of Harrison and Wood (1949) indicates that the capacity of the coronary arteries is directly related to the weight of the heart and that the cross-sectional area of the coronary arteries increases in hypertrophied hearts. They thought that the coronary enlargement keeps pace with the needs of the enlarged heart and that relative ischemia is not a cause of heart failure in hypertension. In *atrophic hearts*, the muscle fibers have a diminished diameter and their number may be decreased (Karsner *et al.*,

1925); consequently, the capillary concentration is increased.

Visualization of Coronary Arteries During Life. According to Snellen and Nauta (1937), calcification of the coronary arteries may be recognized with the fluoroscope by dancing shadows seen in locations corresponding to those of the arteries. In 5 patients, the x-ray diagnosis was confirmed at necropsy.

Radner (1945) injected Thorotrast into the ascending aorta in 5 persons, and Jonsson (1948), contrast medium through a catheter in 5 persons, with indifferent results. Gordon and associates (1950) were able occasionally to visualize one or more of the coronary arteries in angiocardio-graphic examinations following the intravenous injection of Diodrast. The visualization was clearer in infants and children when examined under an anesthetic. Pearl and associates (1950) devised an apparently safe method of coronary arteriography in the dog. They inserted a specially constructed catheter, through a peripheral artery, into the aortic sinus, injected 4 ml. of 70 per cent Diodrast and regularly outlined the coronary arteries. Electrocardiograms taken during the procedure were normal. Thal and his associates (1957) performed 18 consecutive coronary arteriograms on persons with no untoward reaction. Under local anesthesia, the aorta was entered through the right brachial artery. The tip of the catheter was positioned about 2 inches above the sinuses of Valsalva and radiopaque media was injected within a period of 1.5 seconds, using an injection block. Multiple films (5 exposures per second) were taken. This study appears to be promising in the development of a practical method of coronary arteriography.

CORONARY ATHEROSCLEROSIS

Terminology. There is a certain looseness in terminology with reference to degenerative disease of the coronary arteries.

Clinically, this may in part be excused, inasmuch as one may not be certain of the exact pathologic lesion present. *Angina pectoris* is a clinical term (see definition, page 1011) having reference to cardiac distress, particularly pain or dyspnea, usually of a temporary or transient nature, resulting from relative myocardial anoxia. This is usually induced by exertion, eating of

meals, excitement, or exposure to cold. The commonest pathologic findings in *angina pectoris* are narrowing or occlusion of one or more arteries, old myocardial fibrosis, stenosis of the coronary ostia resulting from syphilitic arteritis, or cardiac hypertrophy usually of severe degree. Coronary insufficiency (Levy and Bruehn, 1936) and coronary failure (Freedberg *et al.*, 1948) are other clinical terms which indicate prolonged functional distress and one may then assume that the myocardium is subject to a relatively severe degree of ischemia. Both terms, *angina pectoris* and

acute coronary insufficiency, are used to describe functional states in which the coronary blood flow is not adequate for the needs of the myocardium. Büchner (1939) and Master and associates (1941) have stressed the condition of *acute coronary insufficiency*, a syndrome of severe myocardial ischemia, more prolonged and more severe than that occurring in angina pectoris, but with clinical signs less severe than in acute myocardial infarction. It is frequently accompanied by transitory electrocardiographic changes (particularly by depression of the ST segment) and often gives rise to focal areas of myocardial necrosis, especially in the subendocardial layers and in the papillary muscles of the left ventricle. Scherf and Golbey (1954) pointed out that the term acute coronary insufficiency or acute coronary failure should not be used to indicate a definite disease entity, but to describe a symptom.

Pathologic terms applying to coronary arterial disease include coronary atheromatosis, sclerosis, atherosclerosis or arteriosclerosis; coronary narrowing, coronary thrombosis, and coronary occlusion, myocardial ischemia, infarction and fibrosis. Coronary occlusion and myocardial infarction may exist independently of each other. Blumgart and co-workers (1941a) stated that the syndrome called "coronary occlusion," consisting of prolonged subternal oppression or pain, a fall in blood pressure, pallor and other manifestations of shock, electrocardiographic changes, fever, leukocytosis and increased sedimentation rate, really signifies *myocardial infarction*. Since *coronary thrombosis* can be diagnosed only at autopsy, Yater and associates (1955) suggested that the clinical diagnosis in patients suspected of this condition should be coronary insufficiency with or without myocardial infarction. The term *atheroma* or *atheromatosis* (of an artery) should indicate a degenerative lesion in which lipid material, particularly cholesterol, is accumulated in the intima. This condition may be reversible. The designation *arteriosclerosis* has been applied to a variety of diseases of the arteries and arterioles, and it has also been used synonymously with atherosclerosis. It is characterized chiefly by fibrosis or hyalinization and sometimes also by calcification, particularly in association with atheromatous deposits, the

latter deposits being either primary or secondary to the sclerotic changes. Arteriosclerosis frequently develops in association with an area of inflammation and, in such cases, ordinarily reveals no atheromatous deposits. The term *atherosclerosis* is preferred. It indicates the presence of lipid material and of reactive connective tissue. The atheroma may be primary or it may be secondary to the sclerotic changes.

Macroscopic Changes

The description of atheromatous and atherosclerotic changes in the coronary arteries has been largely taken from the work of Wolkoff (1929). These changes are similar to those which occur in the aorta (see Chapter XIV) and vary greatly in severity in different persons of the same age. The *degree of atherosclerosis* of the coronary arteries is often *graded* grossly (from 0 to 4) on the basis of the relative amount of atheromatous material deposited, thickening of the walls, and particularly upon the extent of focal atherosclerotic narrowing or occlusion of the lumen.

1. *Atheroma*. The first macroscopic changes occur in the form of yellow, minute (pinhead-sized) spots of lipid material visible beneath the intima, which are round and scarcely elevated above the surface. They were encountered by Wolkoff as early as age 9 (one to three spots in children aged 9, 10 and 11 years); in one-half of the number of persons observed by her during the second decade of life; in two-thirds of those during the third decade of life; and in the coronaries of all persons after their fortieth year. While Monckeberg found this change earliest in the left coronary artery (at about age 15) and claimed that this was generally the site of earliest localization of atheroma in the body, Wolkoff always found such spots in the aorta above the aortic valve and in the mitral valve earlier than in the coronary arteries. In the second and third decades the spots are more numerous, larger, rounded or oval, or occur as streaks, 1 to 2 cm. long, which follow the long axis of the artery. The process, in general, increases in severity with age. Its order

of frequency of localization is: first portion of anterior descending branch, main stem of left coronary, first portion of right coronary, and first portion of left circumflex branch.

Klotz and Manning (1911) encountered fatty streaks in the intima of the aorta most frequently between the ages of 21 and 30 (in 12 of 15 persons) and rarely (only once in 10 persons) after the age of 50. They believed that many of these superficial lesions disappeared almost entirely, leaving the artery "in an elastic condition equal to normal."

2. *Fibrous plaques.* Beginning at about age 30, the fatty spots, in part or whole, become covered by hyaline-like connective tissue, forming rounded or irregular plaques of white color which encroach upon the lumen. These also make their appearance first in the left coronary, the order of localization being the same as that of the lipid deposits which precede them. Fibrous plaques may be encountered without accompanying lipid deposits and, in such cases, one may not always be able to determine if the fibrosis was preceded by lipid deposits or if it was a primary change. Indeed, Duguid (1946, 1955) has revived the hypothesis of Rokitsansky by suggesting that coronary atherosclerosis, especially of the type in which narrowing of the lumen is associated, can be more satisfactorily explained as a late *sequel of coronary thrombosis*. As a result of histologic studies, Duguid believes that all the features of atherosclerosis, with fibrous intimal overgrowth and deposition of fat, can be produced by organizing thrombi. In these cases, fat is deposited as a result of softening and fatty degeneration of red blood cells and fibrin within thrombi. Although there is no doubt that atherosclerosis and certain stages of organizing arterial thrombi are often indistinguishable, the importance of thrombosis as a cause of coronary atherosclerosis still remains to be determined.

In middle age or later, the coronary arteries and their main branches, therefore, frequently show scattered plaques, often with points of narrowing of the lumen, particularly at sites of arterial branching; at such points of constriction, thrombosis is favored. There may be more or less diffuse atherosclerosis with thick-

ening and rigidity of the wall. Such rigid vessels often have narrow lumina; at other times the lumina are wider than normal, as a result of loss of elasticity, presumably because of age, and the vessels are tortuous. Thus, sclerosis may be focal or diffuse, present with or without narrowing of the lumen and with partial or complete occlusion.

3. *Calcification.* In later decades, rarely before 40, the plaques may become calcified, or they may show ragged ulceration of the intimal surface, frequently with secondary *thrombosis*.

Localization of Coronary Sclerosis. The localization of atherosclerosis in the coronaries is earliest and most severe in the first portion of the anterior descending branch of the left coronary and in the main stem of the left coronary artery; next, in the first portion of the right coronary artery and then in the first portion of the left circumflex branch. In only 5 of 120 hearts studied by Wolkoff (1929) were atherosclerotic changes more severe in the right coronary than in the left, and in 4 of these the left circumflex branch was poorly developed and its function largely taken over by the right coronary. Atheromatous foci also are seen particularly on the portion of the wall that lies adjacent to the epicardium; such foci are also prominent in the main vessels at sites of branching.

According to Geiringer (1951a), however, atheroma rarely occurs in stretches of the anterior descending coronary artery which are covered by myocardium. Geiringer found that this vessel was covered, in part or all of its course, by myocardium in approximately one-fifth of human hearts, and he designated such arteries as *mural coronaries*. Edwards and associates (1956) encountered intramural coronary arteries in 15 hearts (left anterior descending in 13, right coronary artery in 1, and left circumflex branch in 1) among 276 unselected consecutive autopsies. They concluded, in contrast to Geiringer, that the covering of a main coronary artery by myocardium failed to protect it from atherosclerosis.

Relative severity of sclerosis in other arteries. Sclerosis of the coronaries generally precedes sclerosis of other arteries of the body. In men under 40, Dock (1946) found that coronary sclerosis was usually not associated with sclerosis of the



Figure VIII-5. Atheromatous deposits in deeper layers of intima. Note atrophy of media in right lower portion of figure. X120. Elastica-van Gieson. (WCGH, 40 A 115.)

aorta or cerebral or tibial arteries. Munck (1946) compared the degree of atherosclerotic changes in the coronaries, aorta and cerebral arteries in 396 persons who died suddenly from the effects of coronary sclerosis. He found that sclerotic changes in the left anterior descending branch were relatively more advanced than in the aorta or the arteries of the brain. Morgan (1957), in a study of 20 cases of advanced coronary artery disease, compared atherosclerotic lesions in the thoracic and abdominal aorta, renal artery, brachial and popliteal arteries with lesions of the coronary arteries. He concluded there was no obvious relation between atherosclerosis generally and the severity of coronary occlusion.

In an analysis of the gross pathologic findings in 80 fatal cases of coronary atherosclerosis among soldiers 20 to 36 years of age, French and Dock (1944) found atherosclerotic lesions present in more than one of the main coronary branches in 67 hearts. The most important stenosing lesion was found in the anterior descending branch of the left coronary in 63 hearts, in the right coronary artery in 11 hearts and in the circumflex branch of the left coronary in 6 hearts.

Severity of coronary sclerosis according to sex and age by decades. White and associates (1950) sectioned the coronary arteries and their main branches at intervals of 3 mm., and measured the degree of sclerosis, in the hearts of 100 men in each decade between the ages of 30 and 89. Ackerman and co-workers (1950) made a similar study of the hearts of 100 women in each of these

six decades. In both studies, in nearly every decade, the degree of sclerosis was greatest in the anterior descending branch of the left coronary and less severe in the following arteries, in the order named: right main coronary, left circumflex branch, stem of left coronary, right posterior descending and right marginal branch. As a rule, the degree of sclerosis in each of the six vessels examined was greatest in the proximal third, less in the middle third and least in the distal third.

Comment. The greater involvement of the anterior descending branch by atherosclerosis may possibly be related to a relatively greater traumatizing effect of the blood which flows at an angle of approximately 180 degrees to that in the ascending aorta while the flow of blood both in the right coronary artery and the left circumflex branch is approximately at right angles to that in the ascending aorta.

Microscopic Changes

1. Early deposition of lipid material. Even before the fatty spots become grossly visible on the intimal surface, lipid material staining with Sudan III is demonstrable in the deeper layers of the intima (Figure VIII-5). The ground substance in this layer does not then show the pale rose color with van Gieson's stain as normally; at these sites the lipid material is deposited focally, causing separation of the elastic fibers. The deposits of lipid accumulate, causing elevation of the surface of the intima, and they may also encroach upon the media. The lipid also frequently infiltrates the cells of the intima, sometimes those of the media, and occasionally even those of the adventitia.

2. Intimal connective tissue. As early as age 15, a connective tissue layer is demonstrable in the intimal zone on the inner aspect of the hyperplastic layer about focal sites of lipid material. Some of these connective tissue cells may be infiltrated with lipid. Bork (1926) found that comparable changes did not develop in the aorta until age 25 and in the femoral artery until 40 years of age.

3. Atheromatous foci and fibrous plaques. As early as age 20, the lipid foci may be associated with, or converted into, plaques of fibrous or hyaline connective tissue and some

of the lipid material may be resorbed (Klotz and Manning, 1911; Anitschkow, 1933). The fibrous plaques occur on the inner aspect of the elastic-hyperplastic layer and consist of wide bands of hyalinizing fibers which stain bright red with van Gieson's method. At times these hyaline fibers may surround a focus of fatty material. The fibro-lipoid plaques may become exceedingly thick, even up to 10 or 20 times the thickness of the media. They may encroach upon the lumen and even occlude it, but the general structure of the musculoelastic and elastic-hyperplastic layers is usually maintained. The lipid foci and the fibrous plaques may stretch the elastic fibers of the media and may cause atrophy of this layer.

4. *Vascularization of Intima.* A number of investigators (Wolkoff, 1929; Leary, 1934; Paterson, 1936; Winternitz *et al.*, 1937; Wartman, 1938) have observed capillaries arising from the intimal endothelium of an athero-

sclerotic coronary artery, with or without thrombosis. Paterson found such vascularization of the intima to be common in thrombosis of coronary arteries.

5. *Ulceration, thrombosis, calcification, ossification.* In advanced cases of atheromatous deposits, one may encounter cholesterol crystals which are enclosed in other lipid material or are present within the fibrous tissue of a plaque. The intima may become ulcerated and the seat of thrombi. In large fatty foci or in fibrous plaques, calcium may be deposited, as early as age 40; occasionally ossification may occur, usually at sites of previous calcification. The ossified tissue may contain bone marrow.

6. *Organization. Hemorrhage of capillaries.* Beginning at age 40, in about 50 per cent of persons, there is an ingrowth of blood capillaries into the atherosclerotic plaques. In advanced coronary sclerosis, such vascularization is constantly present (Leary, 1938).



Figure VIII-6. Portion of wall of atherosclerotic coronary artery. Note thick hyalinized intima containing cholesterol. Organization is present in the intima and in the atrophic media. X 150. (WCGH, 40 A 160.)



Figure VIII-7. Organization and inflammatory cell infiltration in walls of atherosclerotic coronary artery. Intima is at upper portion of figure. X 200. (WCGH, 55 P 191.)

These vessels come principally from the vasa vasorum in the adventitia and outer half of the media but also may spring directly from the lumen of the coronary artery. Newly formed capillaries are bordered by lipid macrophages. There is also usually associated an infiltration of lymphoid cells (Figure VIII-6), principally in the adventitia, but also in the media (Figure VIII-7) and even in the intima. The infiltration is often perivascular. The adventitia becomes thicker and more fibrous. Sometimes the capillaries rupture and the resulting hemorrhage may extend to the lumen and lead to formation of an obstructing thrombus.

Geinnger (1951b) made serial sections from 300 aortas and from the first inch of the anterior descending branch of the left coronary artery of 100 hearts. He found that coronary thrombosis usually occurs over an ischemic, necrotic, atherosclerotic plaque and that it is often associated with hemorrhage within the plaque.

Moon and Rinehart (1952) studied the microscopic appearance of the coronary arteries in 250 persons with coronary atherosclerosis. They listed their findings in the following stages. (1) *early sclerosis*, characterized by (a) subendothelial fibroblastic intimal proliferation, (b) increased amounts of mucoid ground substance in the intima and occasionally in the media, and (c) fragmentation and destruction of the internal elastic membrane; (2) *moderate sclerosis*, as determined by (a) formation of collagen fibers in intimal

plaques, (b) regeneration of elastic tissue from the mucoid substrate, and (c) deposition of lipid and cholesterol; and (3) *severe sclerosis* characterized by (a) "hyaline degeneration" of fibrous connective tissue, (b) deposition of calcium, and (c) intramural hemorrhage and thrombosis.

Types of atherosclerosis related to age. It must be noted that many of the atherosclerotic changes in the intima occur concomitantly with changes which are attributable to age. von Albertini (1955) noted that atherosclerosis is not a cause of aging but becomes intensified by the aging process. He distinguished between two types of atherosclerosis: the wide type, generally found in old people, and not causing organic complications; and the narrow type, usually found in young people, causing local stenosis and often having serious consequences.

In the presence of atherosclerosis of the larger coronary vessels, the *small intramuscular branches* may show similar mild lesions but in most instances they are entirely free from such changes.

Microscopic Grading of Coronary Sclerosis. Table VIII-1 lists the principal microscopic features in early, moderate and advanced (grades 1, 2 and 3) coronary sclerosis, based on the findings of Yater and associates (1948c). Note that no mention is made of the caliber of the lumen. Although narrowing of the lumen is usually the result of its encroachment by the thickened atheromatous intima, severe sclerosis may be present in association with a lumen of normal caliber, or with one that is actually dilated owing to ectasia caused by aging. In coronary sclerosis, inasmuch as damage to the myocardium is principally related to the degree of narrowing of the arterial lumen rather than to the degree of atherosclerosis *per se*, the severity of each of these changes should be noted. Therefore, in any given artery, one should indicate both the degree of sclerosis and the degree of narrowing. If the vessel is occluded by atherosclerosis, one should, in addition, indicate whether fresh thrombosis is present or absent.

Minkowski (1947) photographed microscopic sections directly on enlarging paper and calcu-

lated the ratio of intima to media. White and associates (1950) microscopically graded the coronary vessels on the basis of reduction of the size of the lumen as compared with the thickness of the wall, grade 1 indicated minimal sclerosis and grade IV, complete atherosclerotic closure of the lumen. One may likewise grade coronary sclerosis on the basis of the severest degree of narrowing of the lumen, grade 1, 2, 3, and 4 representing narrowing of the cross-sectional diameter of 25, 50, 75 and 100 per cent, respectively. Lober (1953) graded coronary sclerosis from 0 to grade IV, on the basis of the microscopic examination of the most severely affected area, taking into consideration: (1) the degree of *infiltration of the intima*, (2) relative *area of lumen*, (3) relative *thickness of intima*, (4) degree of *elastic degeneration*, and (5) *outside diameter of the artery*. He found the following changes: progressive increase in intimal thickness, from 12 per cent in newborn girls to 81 per cent in men of the ninth decade, progressive increase in outside diameter of the artery, from 0.7 mm. in newborn girls to 3.6 mm. in men of the eighth and ninth decades, progressive increase in degree of sclerosis, from birth through seventh decade in both sexes, and progressive decrease

in area of the lumen, from 62 per cent of total area of artery in newborn to 21 per cent in men of ninth decade. He concluded that it was relatively immaterial whether intimal thickness, relative size of lumen, or degree of infiltration of the intima was taken as the basis for estimating the degree of coronary sclerosis. He regarded age as an important factor since the coronary sclerosis progresses at a nearly uniform rate with age. The degree of sclerosis was greater in persons with evidence of *hypertension* than in those without hypertension, and significantly less in persons who died with *malignant disease* than in those who did not have cancer.

Gore and Tejada (1957) classified atherosclerotic lesions according to the percentage of intima involved and also according to the following grades: grade 1, lipid streaks, spots and patches; grade 2, elevated, smoothly surfaced, fibrous plaques of variable lipid content, grade 3, plaques with ulceration, necrosis or hemorrhage; and grade 4, calcified plaques.

Development of Collateral Anastomotic Channels. There is abundant experimental

Table VIII-1
Microscopic Grading of Coronary Atherosclerosis
(After Yater *et al.*, 1948c)

Structure or Pathologic Feature	Degree of Atherosclerosis		
	Grade 1: Early	Grade 2: Moderately Advanced	Grade 3: Advanced
I. Atheromatous plaque			
1. Connective tissue	Loose; young fibroblasts	Hyalinized at base	Hyalinized at base and surface
2. Amorphous material	Little or none	Much cholesterol or lipid	Much cholesterol or lipid
3. Cholesterol	Few or no crystals	Few clefts	Many clefts
4. Vascularization	Slight or none	Slight, marginal	Abundant, marginal and basal
5. Calcium	None	Minimal	In masses
II. Internal elastic lamina	Slight to moderate damage	Fragmented or absent	Severely damaged or absent
III. Media beneath plaque			
1. Thinning	Slight	Moderate	Media atrophic
2. Loss of muscle fibers.....	Little or none	Moderate	Moderate
3. Fibrosis	Minimal	Increased	Increased; hyalinization

and anatomic evidence that partial or complete occlusion of a coronary artery is followed by enlargement of pre-existing anastomotic vessels and development of new anastomotic channels which then help to supply the anemic or ischemic area with blood. Leary and Wearn (1930) reported 2 cases of complete occlusion of both coronary ostia by syphilis (in patients aged 35 and 20) and explained the ability of these patients to live and work, by the development of compensatory circulation through the thibesian veins.

Types of compensatory anastomoses. Wiggers (1936) enumerated three types of compensatory anastomoses that may develop after nonfatal coronary occlusion: (1) new inter-coronary communications, (2) extracardiac (pericardial) communications, and (3) enlargement of arterioluminal channels. In atherosclerotic occlusion, or in occlusion of the ostium of one coronary by syphilis, new communications of the first type apparently are of most importance, however, in gradual occlusion of both ostia by syphilis, or of the lumina of both vessels near their ostia by atherosclerosis, life may be maintained by development of the last two types of channels named.

Rate of occlusion. The new or enlarged channels tend to prevent death after a subsequent closure of the same vessel or of another branch (Gregg and Muntz, 1938, Blumgart *et al.*, 1942). The patient is thus better able to withstand the effects of a gradual occlusion of a coronary artery than the effects of sudden occlusion. Blum and associates (1938) gradually occluded the anterior descending branch of the left coronary artery at one point, in dogs, until occlusion became complete at the end of 5 weeks. The resulting collateral circulation was sufficient to prevent a large part of the myocardial damage which occurred if the same artery was suddenly occluded at the same point.

Anastomoses with extracardiac arteries. Hudson and associates (1932), by an injection technique, found widespread anastomoses of atrial branches and coronary branches to the pericardial fat with the pericardiophrenic branches of

the internal mammary arteries and the anterior mediastinal, pericardial, humchal, superior and inferior phrenic, intercostal and esophageal branches of the aorta. The anastomoses between the cardiac and extracardiac vessels were most extensive around the ostia of the pulmonary veins.

Development of anastomoses in response to need. By means of a multicolored injection technique, Schlesinger (1935) demonstrated a rich anastomotic circulation only in those hearts in which there was occlusion of the coronary artery; the compensatory blood usually came from the left ventricle. He concluded that anastomoses develop in the coronary arterial system only when and where there is need for them. He found occlusions of two main divisions of the coronary arteries in 4 of 6 infarcted hearts. More important than the multiplicity of such lesions is the speed of occurrence of occlusion or narrowing. Thus, rapid occlusion of one branch will usually result in infarction, even though other branches are normal. Anastomoses, therefore, develop not as a result of aging, but in response to disease of the heart, particularly atherosclerotic coronary disease. Blumgart (1951) studied over 1600 hearts with the Schlesinger technique. In 200 hearts without coronary atherosclerotic or cardiovascular disease from patients who died of non-cardiac disease, no interarterial anastomoses were found, indicating that development of anastomotic channels is not a necessary concomitant of the aging process. Blumgart and associates (1955) occluded the left circumflex artery near its termination, in domestic pigs. They demonstrated that anastomoses began to develop after 2 days and were uniformly present after 17 days.

Multiple sites of occlusion. Saphir and associates (1935) found that, whenever a myocardial infarct was encountered, at least two branches of the coronary arteries supplying the infarcted area were involved; complete occlusion of two of the three major divisions of the coronary arteries was found in 11 of 30 infarcted hearts studied. Holyoke (1945) applied Schlesinger's method of injection in 70 hearts and demonstrated a total of 31 points of occlusion of the coronary arteries in 12 hearts. Inter-arterial anastomoses were found in all hearts with pronounced atherosclerotic narrowing, but in other hearts only in association with marked hypertrophy.

Size of intercoronary anastomoses. In a study of the coronary anastomotic circulation, visualized by means of an injection method, Blumgart and associates (1940) found no intercoronary anastomoses larger than 40 micra in diameter in normal hearts. In hearts with obstruction to the coronary blood flow by atherosclerotic narrowing or occlusion, they regularly demonstrated intercoronary anastomoses which measured 40 to 200 micra in diameter. Prinzmetal and associates (1947) demonstrated anastomotic vessels between the two ventricles by perfusion of the heart postmortem with radioactive phosphorus bound to erythrocytes, and by injection of one of the coronaries with glass spheres of known size. The anastomoses between the intercoronary arteries measured from 70 to 180 micra in diameter, the arteriovenous anastomoses ranged from 70 to 170 micra, and the anastomotic channels between coronaries and the ventricular cavities measured from 70 to 220 micra. Any one or all of these routes of collateral circulation may function following coronary occlusion, and may be a factor in limiting the size of myocardial infarction following obstruction of a major coronary artery. Zoll and associates (1951) used Schlesinger's technique in a study of 1050 hearts, injecting an agar-lead mass whose particles did not enter vessels smaller than 40 micra in diameter. They demonstrated anastomotic channels having a diameter over 40 micra in only 9 per cent of grossly normal hearts from non-anemic patients, as compared to 39 per cent of grossly normal hearts from anemic patients; and in 74 per cent of hearts with recent occlusion, and in 100 per cent of hearts with old occlusions only. Thus, collateral anastomoses develop in response to relative cardiac anoxia, particularly in severe coronary sclerosis. In animal experiments, they were able to produce intercoronary arterial anastomoses in 4 to 12 days by partial narrowing of a coronary artery.

Nourishment of different portions of ischemic myocardium. After ligating a coronary artery in the dog, Prinzmetal and associates (1948) perfused the heart with radioactive erythrocytes. They determined the relative volume of blood in the ischemic and non-ischemic portions of the subendocardium and subepicardium, both in the left ventricle and in the right ventricle. In the left ventricle, the volume of blood in the ischemic subendocardial tissue was two-thirds that of the adjacent non-ischemic myocardium, while the volume of blood in the ischemic subepicardial

tissue was equal to that of the adjacent non-ischemic portion. The relatively poorer nutrition of the subendocardium, compared to the subepicardium, thus explains its greater involvement in myocardial infarction in the left ventricle. On the other hand, in the right ventricle, following coronary ligation, both subendocardial and subepicardial portions of the regions supplied by the ligated vessel contained volumes of blood equal to those in non-ischemic regions. Thus, in coronary occlusion affecting the myocardium of the right ventricle, the nutrition is better than in occlusion affecting the myocardium of the left ventricle. This explains the rarity of infarction of the right ventricle.

Etiology and Pathogenesis

Coronary Arterial Disease in Infants and Children. Clinically significant atherosclerosis of the coronary arteries, so commonly encountered in adults, is decidedly rare in infants and children.

One of the youngest patients reported to have died of atherosclerotic coronary occlusion (Jokl and Greenstein, 1944) was a 10-year-old boy. The left descending branch was almost completely occluded by an organized thrombus for a distance of about an inch, beginning one-half inch from the orifice of the vessel. Five other instances of sudden death from coronary arteriosclerosis in children, ranging from 12 to 15 years of age, are listed by Rigdon and Willeford (1950). (See also reference to fatal atherosclerotic occlusion in an 8-year-old boy with xanthoma tuberosum, pp. 572 and 573.)

The commonest lesion of the coronary arteries encountered in infants and children is termed *medial coronary sclerosis* (Brown and Richter, 1941) or medial calcification with fibroblastic proliferation of the intima (Stryker, 1946a). Brown and Richter found calcification chiefly of the internal elastic lamina. With the calcification there is frequently a co-existing internal fibroblastic proliferation which may lead to occlusion of the vessel. They suggested that a disturbance of calcium and phosphorus metabolism may be at fault.

One of Stryker's patients, a 3-month-old infant, had complete occlusion of one coronary artery, except for small foci of canalization, and small areas of recent myocardial infarction. Stryker

(1946b) found that calcification affected the region of the internal elastic layer, sometimes was present on both sides of this layer, but had a greater tendency to affect the wall on its internal aspect. In each of 5 children, arteries in other organs of the body were similarly involved. He pointed out that this condition must be distinguished from Monckeberg's sclerosis in which calcific deposit lies in the media proper and is limited by the internal elastic lamina. One of Stryker's (1946b) infants with the disease was stillborn. Menten and Fetterman (1948) reported the condition in 2 siblings. Of 93 reported cases of medial sclerosis involving the coronary arteries, 19 were in males, 12 were in females, and in 2 the sex was not stated (Sladden, 1952). In some cases renal rickets has been thought to be of etiologic importance; other factors that have been proposed include infections, allergy, and hypervitaminosis D.

Other causes of occlusive disease of the coronaries in infancy and childhood include rheumatic arteritis, polyarteritis (periarteritis) nodosa (Sinclair and Nitsch, 1919), and embolism, chiefly from bacterial endocarditis; and more rarely, congenital abnormalities, hypertension and syphilitic arteritis.

Incidence and Severity of Coronary Sclerosis in Relation to Age and Sex. With the span of human life increasing, the incidence of coronary sclerosis is apparently increasing. The incidence of coronary atherosclerosis is far greater among men and, before age 60, more severe than in women.

Rossle (1919, quoted by Karsner, 1933) found that, among soldiers in World War I, the incidence of coronary sclerosis at autopsy rose steadily from 10.6 per cent in the age period 15 to 20, to 50 per cent during the period 45 to 50. Levy and associates (1934) found lesions of coronary arteries in 25.9 per cent of 2877 consecutive autopsies. In one-half of these autopsies, the lesions were slight or moderate, in one-half severe. Coronary sclerosis was present in 19 per cent of persons in the age group 25 to 44, in 40 per cent in the group 45 to 60, and in 60 per cent of those past 65 years. Gordon and associates (1939), in a study of 3400 consecutive autopsies, found a steady increase with age periods in the incidence of coronary sclerosis (a) without narrowing, (b) with narrowing, (c) with partial occlusion, and (d) with occlusion. Clawson (1941) reviewed

the protocols of 30,265 autopsies and determined that in 4678 persons death was attributed to heart disease. Among these 4678 persons, coronary sclerosis was present in 25.9 per cent. Willis and associates (1933) reviewed protocols of 5060 consecutive autopsies and found that coronary sclerosis increased steadily with age in both sexes. Among 188 female children in the first decade, the heart in 92 per cent showed no sclerosis and the remaining 8 per cent had only grade 1 sclerosis, while all 78 women aged 70 or over showed some sclerosis, in most cases of moderate or severe degree. In the eighth decade 3 per cent had grade 4 sclerosis and in the ninth decade, 11 per cent had grade 4 sclerosis.

Grading of coronary sclerosis according to sex and age by decades. White and associates (1950), in their study of cross-sections at 3-mm. intervals of the coronary arteries of 100 hearts of men from each decade between the ages of 30 to 89 inclusive, found that the greatest degree of sclerosis in each of six branches occurred in the decade 50 to 59, at which period 75 per cent of hearts showed severe sclerosis of one or both coronary arteries. In the age period 30 to 39, 18 per cent of hearts had, at some site, sclerosis of grade 3 or 4 (on the basis of 0 to 4), and beyond age 49, most men had grade 3 sclerosis at some point in either or both coronaries. Ackerman and associates (1950), who made a similar study of 600 hearts of women, found that the severity of sclerosis increased for each decade to a maximum in the eighth and ninth decades, when 60 per cent of hearts showed severe coronary sclerosis (grade 3 or 4) at some point in either coronary or in both coronaries. A comparison of the findings in these two series indicates that coronary atherosclerosis was more severe in men, especially before the age of 60.

Death rate from atherosclerotic heart disease according to sex and race. In 1955 the death rate from atherosclerotic heart disease (in the U.S.) was 75 per cent higher among men than among women (*National Vital Statistics*, Washington, D.C., 1957). Lew (1957a, b) reported that in 1954 and 1955, at ages 35 to 44, white male death rates were approximately 6.6 times those for females. This ratio gradually decreased until at age 85 and over, the death rate for atherosclerotic heart disease of the two sexes was about equal. The age-adjusted death rate among white males, from atherosclerotic heart disease, was 2.2 times

that for white females. Among non-white persons, the age-adjusted death rate from atherosclerotic heart disease for males was only 1.5 that for females and the sex-ratio varied very little with age.

Race. Most American writers who have statistically analyzed the racial incidence of coronary atherosclerosis, coronary thrombosis and myocardial infarction, as checked at autopsy, have found these lesions to be less common in Negroes than in white persons. (See Hedley, 1935, 1939, Fitzgerald and Yater, 1946; Moritz and Zamcheck, 1946, Yater *et al.*, 1948a.) Yater (1951), in a study of autopsied cases, found that, of 635 soldiers who had been on active duty in World War II, only 3.8 per cent were Negroes as compared to the army population of 10 per cent of Negroes. According to Lev (1957), the death rate from atherosclerotic heart disease among non-white males is close to that of white males at ages under 45, beyond age 45, the reported lower mortality rate for non-white males may be attributable to poor reporting.

During the 15 years prior to 1957, the death rate from atherosclerotic heart disease has increased much faster among non-whites than among white persons (Lew). This may reflect largely the increasing access to more advanced medical practice, of the non-white population as it has migrated from the rural south to northern cities. In sharp contrast to the situation among males, the mortality rate from atherosclerotic heart disease of non-white women is 4 times that of white women at ages 35 to 44 and more than 2½ times at ages 45 to 54. On the other hand, it is generally recognized that Negroes have a higher incidence of essential hypertension and of syphilitic aortitis and its complications, and that death from these causes is relatively commoner among Negroes than among white persons. Furthermore, the average age at death among Negroes is lower than that of white persons. The expectancy of life at birth in 1955 in the United States was 69.5 years; for white men, 67.3 years; for white women, 73.6 years; for non-white women, 65.9 years; for non-white men, 61.2 years (*Statistical Bulletin, Metropolitan Life Insurance Co.*, July, 1957).

Bruenn, Turner and Levy (1936), in their series of patients with coronary sclerosis, found a ratio of white to colored patients of 12 to 1. They

thought that angina was rare in the colored race, probably, in part, because of the rarity of advanced sclerosis in the Negro. Blache and Handler (1950) found that the incidence of coronary thrombosis at autopsy among 2963 Negroes was only 1.1 per cent, as compared to 17.9 per cent among 1961 white persons. They studied segments of the coronary arteries by staining of elastic tissue and by microincineration, and concluded that the rate of development of coronary atherosclerosis in the Negro lags behind that of the white person by approximately a decade, for the fourth to sixth decades inclusive. They related this lower incidence to a greater tendency of the elastic tissue of the coronary arteries to swell but a lesser tendency to fragment and calcify.

The statement that atherosclerosis is less frequent among Chinese than among persons of the white race apparently has not been proved as yet (Weiss and Minot, 1933b, Gertler *et al.*, 1950).

Familial Tendency. The tendency to develop coronary sclerosis may be familial (Ophuls, 1933b, Bean, 1937). Lew (1957b), quoting from the 1951 Impairment Study of the Society of Actuaries, Chicago, stated that a follow-up study of nearly 18,000 persons, for periods up to 15 years, showed that persons who had reported 2 or more cases of early cardiovascular-renal disease in their families were themselves subject to death rates from cardiovascular disease which were from 1¼ to 2½ times those prevailing among standard risks.

Sudden death, presumably from coronary disease, was reported as occurring in a man at age 42, and three of his sons, at ages 43, 30 and 31 (Herapath and Perry, 1930). The oldest son and one of the younger sons came to autopsy and their coronary arteries showed gross atheromatous changes. In the oldest son, the gross pathologic diagnosis was confirmed by microscopical examination. Fatal coronary disease in homologous twins was reported by Froment and associates (1945). Both developed severe angina pectoris at the age of 34. One twin died at age 35 and at autopsy showed severe atheromatous disease of the coronary arteries with diffuse myocardial degenerative changes. The other twin died suddenly in a spontaneous attack 3 years later. Autopsy was not performed but an electrocardiogram 2 years before death confirmed the clinical diagnosis of coronary disease. Benedict (1958) reported an instance of "coronary insufficiency" in identical female twins aged 44, and cited 6 instances of coronary heart disease in male identical twins in the literature.

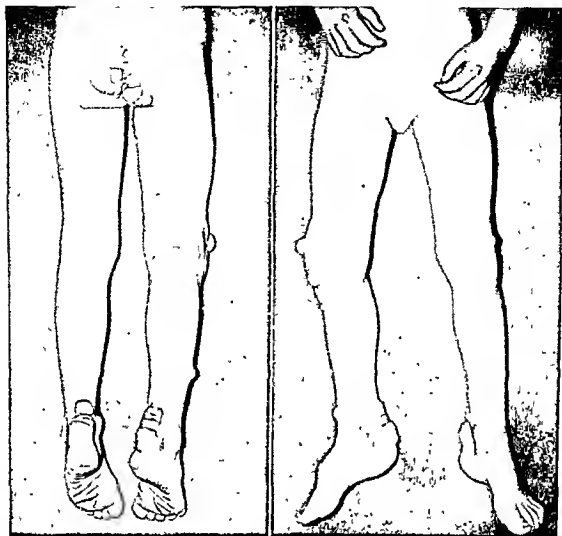


Figure VIII-8 Skin lesions of xanthoma tuberosum in boy 8 years of age. (WCCII, 49 A 460.)

Yater and associates (1948c) believed that *heredity* may be an important factor in the development of coronary artery disease in soldiers under the age of 40, since there was a greater incidence of coronary artery disease in other members of the immediate families of soldiers who survived an attack of myocardial infarction, as compared with the incidence among families in a control group of soldiers.

Xanthoma tuberosum, an inherited disturbance in metabolism of cholesterol, is manifested by hypercholesterolemia and by xanthomatous plaques in the subcutis of the extensor surfaces of the extremities and in various organs, including the aorta and coronary arteries. As a result of the xanthomatous deposits in the coronary arteries, these persons are predisposed to sudden and often prema-

ture death from coronary occlusion (Figures VIII-8 to 10).

Rugdon and Willeford (1950) reported sudden death in a boy of 12. At autopsy both coronaries showed narrowing of the orifices and decided increase in the lumina by atheromatous plaques in the first 2 or 3 cm.; this process was particularly severe in the first portion of the anterior descending branch. In addition, large atheromatous plaques were present in the aorta, innominate, left carotid and left subclavian arteries, and on the mitral valve. The myocardium showed extensive myocardial degeneration but no definite area of infarction. These authors also summarized the findings in 2 other reported cases of xanthoma tuberosum in children. One was a boy 13 years of age with severe aortic and coronary atherosclerosis with pronounced narrowing of the anterior descending vessel and an infarct of the

ventral wall of the left ventricle. The other child was a girl 11 years of age.

An instance of xanthoma tuberosum, that came to my attention, concerned a boy 8 years of age who had had no previous cardiac complaints. On the day before death he collapsed after walking four blocks in the snow. At autopsy, performed 2 hours after death, the cholesterol concentration of the heart's blood was 1000 mg. per 100 ml. In addition to the cutaneous manifestations (Figure VIII-8), the coronary arteries had xanthomatous plaques and were narrowed, and the right coronary artery was almost completely occluded at a point 4 mm. from its orifice. Large plaques were present throughout the aorta but especially in the ascending thoracic portion (Figure VIII-9), the entire circumference of the first 3 cm. of the vessel being involved. Gross xanthomatous infiltrations were seen in the mitral and aortic valves and the endocardium adjacent to these valves, in the ring of the pulmonary valve and the intima of the pulmonary trunk in the region of the commissures of the cusps of this valve; in the mediastinal and mesenteric lymph nodes and in the renal pyramids. There was no gross or microscopic evidence of myocardial infarction. Section of the wall of the coronary artery revealed

changes which were similar to those of atherosclerosis in adults. These consisted of deposits of lipid material, severe thickening by connective tissue which was undergoing hyalinization, formation of new capillaries, and a mild degree of lymphocytic infiltration (Figure VIII-10). There was some atrophy of the media.

Build and Weight of Body in Coronary Atherosclerosis. The belief that thin persons have less tendency to coronary sclerosis than obese persons (Levine and Brown, 1929) is confirmed by insurance tables which show higher death rates among overweight persons for each of the following categories of diseases: organic diseases of the heart, angina pectoris, and diseases of the arteries (Dublin, 1930). Underweight persons have lower rates than persons of normal weight.

A study made by Dublin and Marks (1952) of the Metropolitan Life Insurance Company, of some 50,000 men and women who were charged extra premiums because of overweight and who were followed for periods up to 25 years, showed a 40 per cent higher total mortality for those who were moderately overweight and 65 per cent



Figure VIII-9. Large atherosclerotic plaque of aorta in boy of 8 years with xanthoma tuberosum. Death was caused by severe narrowing of the coronary arteries. The right coronary artery was almost completely occluded by atherosclerosis. (WCGH, 49 A 460.)

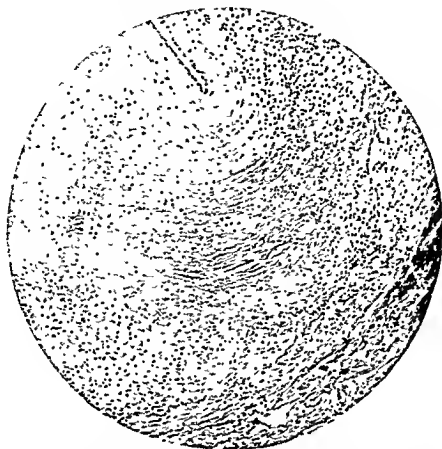


Figure VIII-10 Segment of cross section of right coronary artery in boy with xanthoma tuberosum. Note slitlike lumen and great thickening of intima which shows deposits of cholesterol, considerable fibrous and hyaline connective tissue, and some organization. X100. (WCGH, 49 A 460)

higher mortality for those who were markedly overweight. The bulk of this excess mortality was the result of cardiovascular-renal diseases, primarily of atherosclerotic origin. This study also showed that persons who had reduced their weight sufficiently to be eligible for standard insurance premiums, had a virtually normal mortality rate. Bahr (1938), in a study based on 308 autopsies, also found coronary sclerosis more frequently among florid and robust persons than among asthenic persons. On the other hand, Bean (1937) did not find such a correlation in his study of 300 cases of myocardial infarction. Similarly, Yater and associates (1948a) studied the autopsy records of 450 soldiers under the age of 40 who died from coronary artery disease, and found that obesity was not a factor of any importance. Faber and Lund (1919) studied the influence of obesity on atherosclerotic changes in 408 aortas. They determined the dry weight of the aorta after removing the adventitia, and obtained the concentration of cholesterol and calcium. They found that hypertension is associated

with a concentration of these substances greater than would be expected for the given age but that obesity, in itself, has no effect upon their concentration.

Relation of Coronary Artery Disease to Occupation and Diet. It may be that, in general, occupation does not seem to be an important factor in the causation of coronary sclerosis. Levine and Hindle (1945) found no significant difference between *physicians* and the general population in the average age at death from coronary disease.

An inquiry by Yater and co-workers (1948a) into the case histories of *soldiers* who died suddenly of coronary artery disease revealed a higher incidence among those who had been engaged in *physically less arduous* occupations, such as clerical, professional and supervisory work, than among laborers and farm or factory workers. Keys and associates (1956) studied data on serum cholesterol in relation to *physical activity and diet* in

healthy men in several different countries of the world. They found that the habitual diet, especially its fat content, had much more effect than the physical activity on the concentration of serum cholesterol. The differences in relative obesity did not account for the differences observed in serum cholesterol. According to Katz and associates (1956), population groups that regularly have a diet that is low in calories and in cholesterol lipids tend to have a low serum cholesterol and relatively little coronary atherosclerosis and ischemic heart disease, while the converse is true among those who regularly consume a diet rich in calories and cholesterol lipids. Chapman and associates (1957) studied the clinical incidence of coronary heart disease in Los Angeles over a period of 3 years, among 545 men 40 to 70 years old engaged in sedentary or light jobs and 393 men in the same age group, doing medium or heavy physical work. Applying age-specific rates for both groups, they found no significant difference in incidence of coronary disease. Keys (1957), from a study of occupational and environmental factors in the development of heart disease in various countries of the world, concluded that present indications are that physical activity or its lack is not a major etiologic factor in coronary heart disease or hypertension. Indeed, current opinion holds that physical work does not injure the coronary arteries but, instead, protects them.

Russek and Zohman (1958) clinically studied a group of 100 adults, 25 to 40 years of age, with evidence of coronary atherosclerotic heart disease (89 with classical myocardial infarction and 11 with angina pectoris) and a comparable group without evidence of heart disease, with respect to influence of (a) heredity, (b) obesity and build of body, (c) diet, (d) occupation, and (e) smoking of tobacco. They found that the following 3 major factors predisposed to the development of coronary heart disease: (1) occupational stress (ratio of coronary group to controls, 4.6:1); (2) inordinately high fat diet (ratio of coronary group to controls, 2.7:1); and (3) heredity (ratio, 1.7:1). In addition, smoking was not only more prevalent but also heavier (ratio of 2:1) among the coronary group than among control persons. It was, however, not clear whether nicotine was a predisposing factor or smoking was merely a reflection of the emotional tension.

Seasonal Incidence of Coronary Occlusion.
In the north temperate regions of the United

States, attacks of coronary occlusion occur more frequently during the cold winter months than during the warm summer months. This difference in incidence is probably related to the greater metabolic activity of the body and the greater frequency of respiratory infections during the cold months. Bean and Mills (1938) found that the incidence of cardiac failure from rheumatic disease and atherosclerosis also showed a similar seasonal variation, probably for the same reasons. However, Heyer and associates (1953) found, among 1386 proved cases of myocardial infarction from Dallas, Texas, that attacks occurred more frequently during the hot summer months, when respiratory infections were at a minimum. Thus, it would seem that the incidence of acute myocardial infarction is augmented by exposure to hot or cold weather.

Morbidity and Mortality of Coronary Artery Disease in the United States. In a statistical study of mortality from heart disease among white persons in the United States in 1940, Gover and Pennell (1950) found that the principal types of heart disease causing death at various age periods were as follows: under 5 years of age, congenital heart disease; from 5 to 35 years, valvular heart disease; from 35 to 65 years, diseases of the coronary arteries; and over 65 years, diseases of the myocardium. Undoubtedly, most cases in this last category actually represent diseases of the coronary arteries. The increased number of reported deaths from acute coronary disease in recent years may be attributed to: (1) lengthened span of life; (2) improved diagnosis (with increased accuracy in terminology), and (3) probably an actual increase in incidence and severity of atherosclerosis.

In 1954 the mortality rates per 100,000 from atherosclerotic heart disease, including coronary disease, in the United States, were as follows: white males, 275.2; white females, 127.0; non-white males, 186.3; nonwhite females, 122.8. The sex differences among white persons for atherosclerotic heart disease in the United States are similar to those in England, Canada, and Australia (*Statistical Bulletin*, Metropolitan Life Insurance Co., 38:2, June 1957). In 1955 (National Office of Vital Statistics, Washington, D.C.,

1957) diseases of the heart were responsible for 810,200 deaths in the United States (exclusive of fetal deaths and of deaths among armed forces overseas); cancer, the second leading cause of death, was responsible for 240,681 deaths. Atherosclerotic heart disease, including coronary disease, caused 400,150 deaths. In addition, there were 313,900 deaths listed in the following categories, in which atherosclerosis of the coronary arteries may have been a factor: vascular lesions of the central nervous system, 175,120, non-rheumatic chronic endocarditis and other myocardial degeneration, 66,150, hypertension with heart disease, 72,630. Thus, clearly, atherosclerotic disease of the coronary arteries is now the leading cause of death in the United States. Furthermore, in recent years, along with the extension of the average life expectancy at birth, the total number of persons and the percentage of those who die of diseases of the heart, and particularly of the effects of coronary sclerosis, have been constantly increasing. During recent years, therefore, increasing attention has been directed to the etiology and control of coronary atherosclerosis.

Coronary Occlusion in Animals. An instance of coronary thrombosis in an 8-year-old female ape was described by Manning (1942). The clinical signs, manner of death, and pathologic changes were comparable to those in coronary thrombosis in man. Crosfield (1944) reported the occurrence of coronary thrombosis in a 3-year-old Ayrshire bull, and Gilyard (1944) reported thrombotic occlusion of the middle third of the right coronary artery in a 6 year old West Indian-bred thoroughbred gelding which collapsed after completing a race of more than a mile. Lindsay and associates (1956) reported sudden death in a 47-year-old female Indian elephant from acute cardiac failure secondary to pronounced atherosclerosis of many small coronary arterial branches. Highman and Altland (1949) found thrombotic coronary occlusions and extensive myocardial infarction in one of their rats that died after being exposed to an altitude of 25,000 feet for 4 hours daily for several months.

Histogenesis of Atheromatosis. Leary (1941) believed that lipid-carrying macrophages are attracted to the intima by chemotaxis, penetrate the endothelium and deposit the lipid material in the intima. The general opinion, however, holds that lipids are de-

posited in the intima before the lipophages appear. Winternitz and associates (1938) attributed the primary change to hemorrhage from rupture of new capillaries that arise from the vasa vasorum or directly from the lumen. Generally, when hemorrhage is found in association with atherosclerosis, it probably does not precede but rather follows the onset of atherosclerosis. With increasing age, there is an accumulation in the intima of lipids which are precipitated in the ground or cement substance, with the formation of cholesterol crystals. Later, fibrous proliferation with or without scarring, vascularization, hemorrhage, inflammatory cell infiltration or calcification may occur.

Duguid (1946) has presented evidence that coronary thrombosis may be followed by fatty degeneration in the thrombus. He (1954) believes that *atherosclerosis may arise* by two different processes: (1) *from deposition of lipids or lipid-bearing cells*, and (2) *from mural thrombi*. The diet may be important in the initial phase, since it may affect the coagulability of the blood or cause fatty changes in the wall and thus promote mural thrombosis. His *encrustation theory* (1955), originally proposed by Rokitsansky, assumes that atheromata are the result of deposition of fibrin on the intima, mural thrombosis, and organization by endothelium with formation of new capillaries from the lumen. This process leads to crescentic thickening at one or many foci. As a result of retarded organization of the thrombus containing blood, a lipid pool is formed. Recurrent thrombi lead to progressively severe atherosclerosis and narrowing of the arteries.

According to Paterson (1936, 1952), *intimal hemorrhage* is not causative of atherosclerosis because the intima is not normally vascularized; rather, it is a complicating factor which accelerates and aggravates the atherosclerotic process. He found that the capillaries arise from the endothelium of the vessel and not from the vasa vasorum; that they are exceedingly prone to rupture, and may give rise to massive intimal pressure. Hemorrhage was responsible for obstruction in less than 10 per cent of occlusions in Paterson's series. Hamilton (1957) examined the coronary arteries from 100 hearts of unselected adults of various ages. He used a modification of Durlacher's technique and cut multiple or serial sections from representative samples. Mod-

erate (grade III) and advanced (grade IV) atherosclerotic lesions, with well vascularized plaques and amorphous pools of lipid, were present in 63. In 51 of these 63 cases, hemorrhages were seen in the atherosclerotic plaques. In about half of the cases showing vascularization of the plaques, capillaries took origin from the lumen. Intramural hemorrhage was present in 12 of 14 cases showing recent coronary thrombosis. Massive hemorrhage was associated in each of 4 cases with rupture of an atheromatous plaque, he believed that the hemorrhage was derived from the lumen and was in the nature of dissection of the plaque. Hamilton thus supports Duguid's explanation of atheroma.

Pathogenesis of Atheromatosis. Experimental production of atherosclerosis in animals (rabbits, chicks and dogs) is predicated on the belief that altered cholesterol metabolism is important in atherogenesis in man (Katz and Stamler, 1953). The imbibition theory of Virchow attributes the deposition of lipids in the intima directly from the lumen of the vessel by infiltration from the plasma. However, the correlation between concentration of blood lipids and degree of atheroma is none too good. Only a few factors in the pathogenesis of atheromatosis in man are known. The relationships of this process to the metabolism of cholesterol, to the intake of lipids in the diet, cholesterol "antagonists" (iodides, thyroid extract, choline, lecithin), or alcohol, to infections and wasting diseases, to age and local trauma, to heredity, build of body and weight, occupation, emotional factors, hypertension, pre-existing local disease, and to endocrine and metabolic diseases, are only partially understood.

Hueper (1942) injected various *macromolecular compounds*, including proteins, carbohydrates and lipins, into animals and produced changes resembling atheromatous lesions. He believes that these substances cannot be broken down or excreted by the body and that, as a result of disturbances in nutritive and oxidative metabolism of the vascular walls, degenerative lesions are produced which are comparable to cholesterol atheromatosis of man.

Hirsch and Weinhouse (1943) believed that with age there is a significant increase in the media of the free and total cholesterol, phospho-

lipids, galactosides and glycerides, and a marked increase of the calcium content, and that these changes apparently are related to age and do not cause atherosclerosis. The lipids of the intima seem to originate in the plasma rather than in the protoplasm of the cells. Most cases of atherosclerosis in man are not accompanied by hypercholesteremia. According to Katz and Dauber (1945), *elevated serum cholesterol* favors atherosclerosis but is not essential for its occurrence. Boas and associates (1948) believed that the frequent hypercholesterolemia in patients with coronary atherosclerosis suggests an etiologic relationship.

Leary (1931) maintained that *alcoholism* is associated with absence of atherosclerotic changes in the aorta. Eberhard (1936) studied the effect of alcohol on the development of atherosclerosis in rabbits. His findings suggest that alcohol may interfere with the development of atherosclerosis in the aorta. Wilens (1947a) believes that in man the habitual use of alcohol does not have any appreciable effect on production of atherosclerosis.

There is no proof that *overnutrition* is responsible for atherosclerosis in man (Weiss and Minot, 1933a). While obesity and atherosclerosis are often associated, the arteries of obese persons past 50 may be unusually free of sclerosis. In diabetics, on the other hand, it is generally conceded that atherosclerosis occurs earlier and is usually more severe in degree than in nondiabetics of the same age. In diabetes and in multiple xanthomatosis, myxedema and lipid nephrosis, the associated high lipemia and cholesterolemia are often related to the development of atheromatosis and attributed to an endogenous fault in metabolism. Furthermore, it has not been proved that a relatively high protein or a relatively high carbohydrate diet is either responsible for, or prevents the development of, atheromatosis or atherosclerosis; or that a vegetarian diet tends to prevent the development of atheromatosis. Wilens (1947b) found severe atherosclerosis of the coronary arteries in 12 of 24 obese patients aged 40 to 60 years, and in only 2 of 39 poorly nourished persons in the same age group. According to Gertler and co-workers (1950), the level of serum cholesterol is independent of dietary cholesterol within normal limits of digestion and the concentration of serum cholesterol is mainly dependent upon the balance between synthesis and utilization. These observers believe that there is no advantage to be



Figure VIII-11. Extreme degree of atherosclerosis of first portion of left coronary artery in a 13-year-old girl with uncontrolled diabetes mellitus. X2. (Courtesy of Dr. T. Hiratzka, Wayne State University College of Medicine.) (WCGH, 58 P 481.)

gained from imposing a low cholesterol diet on patients with coronary artery disease

Bahr's (1938) patients with cancer or tuberculosis had delicate coronary vessels and Wilens (1947b) found evidence that atherosclerotic lesions are less severe in wasting diseases such as cancer and advanced tuberculosis. Since persons past 50 with advanced tuberculosis or cachexia of cancer frequently have astonishingly little atherosclerosis, it is possible that in these conditions the body has metabolized (either more completely utilized or resorbed) cholesterol material that previously was deposited in the arteries. Wells (1933) pointed out that extensive lipid infiltration of the aorta in youth commonly disappears without leading to atherosclerosis (see also Klotz and Manning, 1911), while sclerotic patches may be found free from lipids. Since it appears that the deposition of atheromatous material in the intima is reversible, it should be possible, within limits, to inhibit the formation of atherosclerosis.

Morrison and Gonzalez (1950) administered choline, a lipotropic substance, for periods of 1 to 3 years, to 115 patients with clinically proved myocardial infarction. They reported that in this group the subsequent mortality rate was significantly reduced as compared with that of a comparable control group of patients.

According to Page (1954), the level of cholesterol in the blood depends more on the total caloric intake and the amount of fat in the diet than on the cholesterol content of the diet, and it probably does not matter whether animal or vegetable fat is ingested. Predisposing factors include heredity, maleness, arterial anatomy, hyperlipemia, hypertension, and aging.

The Committee on Lipoproteins and Athero-

sclerosis of the National Advisory Heart Council (1956) attempted to determine if there was a correlation between serum lipoproteins with flotation rates between 12 and 20 Svedberg units (S_r12-20) and myocardial infarction, and if there was any relationship between the serum concentration of total cholesterol and lipoproteins (S_r12-20) and myocardial infarction. The majority of opinion held that one could not predict from these measurements which individuals would develop coronary artery disease.

Tobian and Tuna (1958) produced significant lowering of the concentration of cholesterol in the serum in 23 patients following ingestion three times a day of corn oil, an unsaturated fat. The reduction in the level of cholesterol was maintained during the entire year in which the oil was ingested.

Coronary Artery Disease in Diabetes Mellitus. Among diabetic patients over the age of 40, coronary sclerosis, angina pectoris and death from coronary disease are as common or commoner in women than in men, but in nondiabetics these conditions are much commoner in men (Stearns *et al.*, 1947). These authors stated that any diabetic person of either sex over the age of 40 can be assumed to have severe coronary sclerosis, especially if he also has hypertension or if he has had diabetes for 10 or more years. The severity of vascular disease in persons with diabetes is related to the duration and degree of control of the diabetes (Root, 1948). Nathanson (1932) found severe coronary sclerosis in 41 of 100 autopsied diabetics (and in 53 per cent of diabetics above the age of 50), as compared with 8 per cent of 250 nondiabetic patients in the same age group. In nondiabetics the ratio of males to females was 3 to 1; in the diabetic series, 1.8 to 1.

Persons with diabetes not only have more severe atherosclerosis (Figure VIII-11), but develop atherosclerotic lesions 10 to 12 years earlier than nondiabetic persons (Warren, 1938). Warren found cardiac infarcts in 16.4 per cent of 440 diabetic patients. This compares with the following incidences of infarcts in unselected autopsies: 4.1 per cent of 1750 autopsies (Benson and Hunter, 1925); 4.9 per cent of 1000 autopsies (Barnes and Ball, 1932); 7.8 per cent of 3559 autopsies (McCann *et al.*, 1950); 11.8 per cent of 5000 autopsies (Gould and Cawley, 1958).

Blotner (1930) reported death from cardiac infarction in 3 diabetics following a rapid fall in blood sugar after administration of insulin, and called attention to the *danger of inducing coronary thrombosis by insulin in the elderly diabetic with vascular disease*. Atherosclerosis of the coronary arteries, as well as of the peripheral arteries, is relatively frequent in young diabetic patients. Shivelhood (1948) reported death with clinical evidence of myocardial infarction in a 12-year-old boy who was known to have diabetes since the age of two years. Permission for autopsy was not obtained. Insulin has prolonged the life of persons with diabetes, more of whom now die from coronary disease than from cerebral or peripheral vascular lesions (Bean, 1937). Clawson and Bell (1949) analyzed the age and sex incidence of fatal coronary disease in autopsies of 49,593 nondiabetic and 1182 diabetic patients. Fatal coronary disease was found to be about twice as frequent in diabetic as in nondiabetic men, and three times as frequent in diabetic as in nondiabetic women. About 4 per cent of men and about 14 per cent of women who died of coronary disease, had associated diabetes. Feldman and Feldman (1954), in a study of 1319 consecutive necropsies of adult persons, found coronary heart disease in 43.8 per cent of diabetics as compared to an incidence of 20.1 per cent in nondiabetics. Ackerman and associates (1950) measured the degree of sclerosis in the coronary arteries in 600 women, including 25 with diabetes. In each decade except the ninth, those who had diabetes showed greater degrees of coronary sclerosis (12 to 45 per cent) than those who did not have diabetes. Analysis of the causes of death among diabetic patients of the Joslin Clinic, Boston, during 1950-1956, showed that heart disease was responsible for nearly one-half of the total (48.7 per cent), and that two-thirds of these deaths (33.4 per cent) were caused by coronary artery disease (*Statistical Bulletin*, Metropolitan Life Insurance Co., March, 1957). W. A. Thomas and associates (1956) studied the incidence of acute myocardial infarction among diabetic patients at autopsy at Barnes Hospital, St. Louis. For the years 1910 to 1954 inclusive, 8183 adult persons came to autopsy. Of this number, 379 (192 men and 187 women) had diabetes mellitus. Acute infarcts were found in 22 per cent of diabetic men and 28 per cent of diabetic women, as compared with 6 per cent of nondiabetic men and 3.9 per cent of nondiabetic women.

Relation of Cardiac Hypertrophy and Hypertension to Coronary Sclerosis. Approximately one-third (35 to 40 per cent) of persons with coronary occlusion have cardiac hypertrophy. Pre-existing hypertension favors the development of coronary sclerosis, sclerosis being more frequent and usually more severe among hypertensive than among nonhypertensive persons (Bell and Clawson, 1928; Master *et al.*, 1939a; Ackerman *et al.*, 1950). Levine and Brown (1929) stated that a previously existing hypertension is probably the most common single etiologic factor in the development of coronary thrombosis. The tendency to coronary sclerosis among hypertensive persons is greater among men than among women (Davis and Klainer, 1940); this is in agreement with the common finding that hypertension in women runs a more benign and protracted course.

Averback (1936) found that most patients with hypertension who died of heart failure (85 per cent in his series) suffered from severe coronary sclerosis while relatively few with hypertension who died from causes other than heart failure (only 10 per cent) showed severe coronary sclerosis. Of 100 consecutive cases of acute coronary occlusion and myocardial infarction studied by Nay and Barnes (1945), 46 had normal blood pressures prior to the coronary occlusion and myocardial failure, 42 had hypertension previously, and in 12 the blood pressure previously was not definitely known. Failure of hypertensive hearts, however, may occur without accompanying coronary disease and may be the result of myocardial weakness which is primarily related to factors concerned with the hypertension and the available blood supply to the myocardium. In persons with hypertension, there is no increase in the number of capillaries supplying the hypertrophied myocardial fibers, as compared to the number present in hearts of normal size (Wearn, 1941). The enlarged muscle fibers, therefore, have a relatively decreased blood supply. Should the coronary arteries become narrowed by atherosclerosis, the nutrition of the muscle fibers is further compromised. The integrity of the myocardium depends upon sufficient nutrition per unit of muscular tissue. This means that, for a given mass of muscular tissue, there must be a sufficient number of blood capillaries and a sufficient supply of oxygenated blood.

Kaunitz (1947) has pointed out that in the adult heart in which the *left coronary artery arises from the pulmonary trunk*, the coronary lumen is dilated, the wall is thinner than normal, the media has a poorly developed muscular layer, and the intima has fibroelastic thickening. The lack of atherosclerosis in such a vessel, coupled with atherosclerosis in the right coronary, would seem to indicate that there is a relationship between intravascular pressure and the development of atherosclerosis, and would help to explain the frequent association of hypertension and severe coronary sclerosis. In this connection it may be mentioned that atherosclerosis of the aorta is generally most severe in the abdominal portion where the intravascular pressure is relatively high.

Effect of Coronary Sclerosis on Development of Cardiac Hypertrophy. Coronary sclerosis, in itself, probably has little influence on the production of cardiac hypertrophy and hypertension. It is believed that, when coronary occlusion leads to heart failure, the subsequent dilatation of the ventricle may be followed by some degree of myocardial hypertrophy but that hypertrophy in such cases is usually not of severe degree.

Aschoff (1933b) did not believe in the existence of atherosclerotic hypertrophy of the heart, while Kaplan and associates (1938) indicated that it was not frequent. French and Dock (1944) were of the opinion that coronary disease causes no significant hypertrophy in the hearts of young men. Davis and Blumgart (1937), however, presented evidence that *coronary sclerosis leads to cardiac hypertrophy*, presumably because impaired nutrition of the myocardial fibers induces stretching and hypertrophy of these fibers. Karsner (1955) states that hypertrophy occurs in infarcted hearts, independently of hypertension, and that it is probably caused by stretching of the remaining living muscle. From their study of the weight of hearts of soldiers who died of coronary disease, Yater and associates (1948c) also concluded that coronary artery disease alone may lead to hypertrophy of the left ventricle. Harrison and Wood (1949) stated that *cardiac hypertrophy is the rule in ischemic heart disease* (coronary artery disease and myocardial infarction) and that it can be correlated with the duration of heart failure. Boas and Boas (1949) reported that they had many patients with normal blood pressure under observation for years, and

had observed progressive *cardiac enlargement develop* in them after *myocardial infarction*. In every such patient, one or more episodes of heart failure followed the infarction.

Relation of Infection to Coronary Sclerosis. In *old syphilitic infection* of the thoracic aorta, one frequently sees superimposed atherosclerosis of a degree rarely encountered in the absence of syphilis. In syphilitic coronary arteritis, only the ostium and the first portion of the main stem of the coronary arteries are involved by the syphilis and there is usually little superimposed atherosclerosis; in the absence of syphilis, atherosclerosis of the main stem of the coronary arteries ordinarily develops at a short distance beyond the ostia.

On the basis of a careful study, Karsner and Bayless (1934) concluded that pre-existing *rheumatic disease* of the coronaries predisposed the vessels to atherosclerosis. Gross and Oppenheimer (1936), however, from an analysis of their own material, were led to believe that these two lesions were independent and unrelated. Myocardial scars of small size may possibly be the result of old rheumatic disease, but they usually represent the effect of atherosclerotic occlusion of small branches of the coronary arteries.

Many writers believe that rheumatic disease has an allergic basis (see Chapter IX). Rich and Gregory (1947) sensitized 45 rabbits to horse serum and in 18 produced "sclerotic" lesions of the branches of the coronary arteries which were comparable to those caused by rheumatic fever. They thought these lesions were similar to those found in disseminated lupus erythematosus and in a large number of other diseases. The inference is that *allergy* may possibly be a factor in man in the production of coronary sclerosis.

Saphir (1936) reported the occurrence of severe atherosclerosis in the coronary arteries which were also the seat of *thromboangiitis obliterans* in a 35-year-old man. He believes that the latter condition may have been a factor in the production of atherosclerosis. There is relatively little evidence that acute or chronic *infections* favor the development of atherosclerosis in the coronary arteries. Saphir and Core (1950) examined sections from multiple blocks of the myocardium and major coronary arteries from 13 male soldiers, ranging in age from 18 to 29 years, who died suddenly and unexpectedly of severe coronary heart disease. In 10 of the 13 patients, the severe coronary sclerosis was associated with evidences

of old inflammation. They thought that the vascular lesions may have been the result of a primary inflammatory process. Saphir and his associates (1956) also raised the question whether the increase in coronary atherosclerosis in the younger persons in recent years may not be associated with hypersensitivity as a result of the common use of antibiotics and other drugs.

Syphilitic Disease of Coronary Arteries. In approximately one-third of patients with syphilitic mesoarteritis, the orifice of one or both coronary arteries is reduced in circumference (Saphir and Scott, 1930, Bruenn, 1934). Bruenn found that the circumference of the orifice of the normal coronary artery was 8 to 10 mm. The ostium of a coronary is more likely to be involved if it is anomalously located above the sinus of Valsalva (Von Glahn, 1923, Martland, 1930).

In 1000 consecutive autopsies, Von Glahn (1936) found that in 80 (8 per cent), one or both coronary arteries arose above the upper level of their respective sinuses of Valsalva (Figure VIII-12). In a series of 133 cases of syphilitic aortitis (Turner, 1950), the orifice of either one or both coronary arteries was involved in 19 hearts. The orifice of the right coronary artery was narrowed in 15 instances and occluded in 2, that of the left coronary was narrowed in 11, and the orifices of both vessels were narrowed in 7. In every instance but one, the involved coronary artery arose either at the upper level of the respective sinus of Valsalva or above this line. Inasmuch as the syphilitic lesion usually stops at the upper level of the sinus, origin of a coronary artery above this level is an important factor in its involvement by syphilis. In Bruenn's series of 39 cases of syphilitic coronary arteritis, the orifice of the right coronary artery was totally occluded in 8 instances, that of the left coronary in one.

Syphilitic coronary arteritis is not limited to the portion of the artery included in the wall of the aorta but may extend 10 to 12 mm. beyond the orifice to produce stenosis or occlusion of the lumen (Moritz, 1931). It rarely extends more than 1 cm. beyond the orifice. Such narrowing of the coronary arteries may gradually progress to the point of complete occlusion, and yet the heart may show no evidence of myocarditis, fibrosis or infarction. The ostia of both coronary arteries were completely occluded in 2 instances reported by Leary and Wearn (1930); the myocardium, however, was of normal appearance, anastomotic

channels enabling the heart to perform its ordinary functions. With extra exertion or emotion, however, these patients are likely to suffer attacks of angina pectoris; they are particularly exposed to the danger of sudden death. Occasionally syphilitic structural changes contribute to myocardial infarction (Bean, 1937) but only in rare cases does syphilitic narrowing of the coronary ostia actually lead to this condition. It occurred in only 3 of 39 hearts with syphilitic coronary stenosis studied by Bruenn, and in 3 of 40 studied by Burch and Winsor (1942). The average age of patients with syphilitic stenosis of the coronary ostia is about 45 years. The condition is commoner among Negroes than white persons, among men than among women. Kobernuck (1947) reported myocardial infarction as a result of gumma of the right coronary artery with secondary thrombosis of the artery. Martland (1930) reported aneurysm of the artery, with rupture in the pericardial sac, and death.

Relation of Thyroid Disease to Coronary Sclerosis. In hyperthyroidism an increased amount of work is thrown upon the heart and usually the heart shows mild to moderate dilatation and hypertrophy. The microscopic changes are nonspecific.



Figure VIII-12. Anomalous origin of right coronary artery with narrowing of ostium of the artery by extension of syphilitic aortitis. (WCGII, 47 A 81.)

In experimental animals rendered hyperthyroid by the injection of thyroxin and in persons with hyperthyroidism, Rake and McEachern (1932) found no specific myocardial lesions. Weller and associates (1932), in a study of 35 hearts from persons with exophthalmic goiter, found a relatively high incidence of (a) myocardial fibrosis (80 per cent) which was not related to vascular obliteration, (b) endocardial sclerosis (89 per cent), and (c) cellular infiltrations (31 per cent). In a control series of persons of the same age and sex, without thyroid disease and with no evidence of syphilis, rheumatic fever, infective endocarditis or severe coronary atherosclerosis, these changes were less frequent (myocardial fibrosis was found in 51 per cent, endocardial sclerosis in 51 per cent and cellular infiltrations in 17 per cent).

Myxedema is commonly associated with increased hypercholesterolemia, coronary sclerosis and an enlarged rounded heart. Caution must be exercised in the therapeutic use of thyroid extract in myxedema, particularly if the patient develops angina during administration of the drug.

Smyth (1938) summarized the findings in 5 cases of myxedema reported in the literature in which autopsy revealed myocardial infarcts. He added a case of his own in which a patient with myxedema and angina pectoris developed myocardial infarction while under treatment with thyroid substance.

Smoking. The effects produced by tobacco (nicotine) vary greatly with the individual (C. B. Thomas *et al.*, 1956) and with the tolerance acquired by habit. It is well recognized that angina pectoris may be provoked by smoking of tobacco (Arai *et al.*, 1951), and it is generally agreed that nicotine is the principal active ingredient. The evidence that has been submitted for an etiologic relationship of tobacco smoking to coronary sclerosis is largely statistical.

English and associates (1940) found an increasing incidence of coronary disease among men 40 to 49 years of age, with increasing degrees of smoking. Dolgoff and associates (1952) found a correlation between coronary disease and heavy smoking of cigarettes among patients below 55 years of age. The average age of the heavy smokers with coronary disease was relatively low

compared with controls. Hammond and Horn (1954), in a clinical study of 187,766 white men between the ages of 50 and 69, reported that a total of 3002 deaths occurred among men who gave a history of regular smoking of cigarettes, the mortality rate being 52 per cent greater among them than among men who had never smoked. The increase in mortality rate was largely attributed to the effect of cigarette smoking in deaths primarily caused by coronary artery disease. Among those who smoked one package or more of cigarettes daily, the 745 deaths represented a mortality rate 75 per cent higher than that among the nonsmokers. Gofman and his co-workers (1955) claimed that among young men, heavy smokers (20 or more cigarettes per day) particularly had a significant elevation in their serum lipoproteins of low density, thereby increasing their risk of death from coronary artery disease by 40 per cent, as compared with nonsmokers. The validity of the relationship of lipoproteins to atherosclerosis, however, has been questioned. Adlersberg and Zak (1952-53), in analyzing the clinical and pathologic features in fatal coronary disease in 50 persons aged 27 to 46 years and in 50 persons aged 60 to 83 years, found 8 heavy smokers in the younger group and none in the older group.

Summary of Factors in Atherogenesis. It appears that a number of factors operate in causing atherosclerosis, including hereditary predisposition; the male sex; constant ingestion of a diet rich in fats and calories; hyperlipemia; diabetes mellitus; hypertension; mechanical factors (increased intravascular pressure, as in the lower abdominal aorta; eddying of stream at sites of branching of arteries); ingestion of substances which are not completely metabolized (macromolecular substances); and local degenerative changes resulting from previous infection (atherosclerosis superimposed on syphilitic aortitis); aging; and possibly excessive smoking of cigarettes.

Coronary Insufficiency. Coronary Occlusion

Pathologic Basis of Angina Pectoris. Blumgart and associates (1950) compared the cardiac findings at autopsy in 177 patients who had had angina pectoris during life with those in 532 persons who had had no clinical car-

diac manifestations. In 90 per cent of the patients with angina, significant coronary sclerosis (narrowing or occlusion) was present; in the other 10 per cent, syphilitic aortitis, arterial hypertension with cardiac hypertrophy, or valvular lesions were held responsible for the angina. Most patients with angina had myocardial fibrosis and enlarged interarterial anastomoses; approximately two-thirds had at least one old complete occlusion of a main coronary artery or of a primary branch. Of the 532 persons without angina, 40 per cent had significant silent coronary disease. The authors concluded that in all their cases the basis for angina pectoris was coronary arteriosclerosis, arterial hypertension, or valvular disease, alone or in combination.

Occurrence of Pain in Coronary Artery Disease. Cardiac pain is generally an indication of relative myocardial ischemia resulting from impairment of the coronary circulation. It occurs in approximately 20 per cent of persons with atherosclerotic narrowing of the coronaries and in approximately 40 per cent of those with atherosclerotic occlusion or thrombosis (Bruenn *et al.*, 1936). Among 177 patients with angina pectoris studied by Blumgart and associates (1950), not a single patient was found free of heart disease. All anginal patients had either coronary (90 per cent), valvular, or hypertensive heart disease. At least one complete occlusion of a main coronary artery or of a primary branch was present in approximately two-thirds of patients with angina. Angina had been present in 52 per cent of patients with coronary occlusion, in 16 per cent of those with valvular disease, in 5 per cent of those with coronary narrowing and in 3 per cent of those with hypertension. Complete occlusion of one or more of the main coronary arteries, however, may exist without giving rise to any symptoms and may be unassociated with any evidence of myocardial damage (Blumgart *et al.*, 1941a).

A history of cardiac pain may be obtained in approximately 95 per cent of patients with fresh or recent myocardial infarction (Yater *et al.*, 1948a), but only in a majority of patients with old infarcts (Kennedy, 1937; Gorham and Mar-

tin, 1938). Nearly all of the patients with fresh myocardial infarction who do not suffer cardiac pain give a history of dyspnea or weakness. Landman and associates (1949) undertook a study of *asymptomatic myocardial infarction*. In checking the clinical history of 255 patients in whom myocardial infarction was encountered at autopsy, it was determined that pain, shock, dyspnea and congestive failure had been absent during life in 28 (11 per cent). An analysis of their data, however, shows that only 9 persons (3.5 per cent) had fresh infarcts without associated cardiac symptoms.

Hirsch and Orme (1947) demonstrated sensory nerve fibers which terminate in the wall of the coronary arteries. They postulated that the stimuli that produce pain in coronary disease arise in arterial and periarterial tissues rather than in anoxic myocardium as is generally held. In painless myocardial infarction, the absence of pain of anginal type is attributed to localized destruction of afferent pain fibers in periarterial plexuses of coronary arteries supplying the ischemic areas of myocardium (Harrison and Resnick, 1950).

Hypoxemic Necrosis following Coronary Insufficiency. Büchner (1939) has described foci of "hypoxemic necrosis" of heart muscle resulting from an acute or chronic deficiency of oxygen (coronary insufficiency). The causes include atherosclerotic stenosis of coronary arteries, syphilitic narrowing of the ostia of the coronary arteries, circulatory shock, aortic insufficiency, severe anemias, subacute carbon monoxide poisoning, breathing air of reduced oxygen concentration, as at high altitudes (15,000 feet and higher), massive pulmonary embolism, and chronic ventricular hypertrophy with decompensation. According to Büchner, the necrotic foci of muscle are of microscopic size, and at first show loss of striations of the fibers, coagulation of the sarcoplasm into a homogeneous mass, and shrinkage of the nuclei. The nuclei then disappear and in the course of about 24 hours, the necrotic fibers become infiltrated with polymorphonuclear leukocytes. The fragmented necrotic material is liquefied by ferments (from the serum) and resorbed, the local connective tissue cells actively proliferate and, in the course of days, the necrotic



Figure VIII-13. Constriction of small coronary artery in woman who developed gangrene of the lower extremities and died in acute heart failure after receiving 4 successive daily injections of ergotamine tartrate intramuscularly. (WCGH, 36 A 1)

focus is replaced by fibrous tissue which forms a small scar. At times the coronary insufficiency, which is responsible for the necrotic foci, is attended by angina pectoris and an electrocardiogram may show depression of the S-T segment below the isoelectric line. The sites of predilection of these necrotic areas are the inner layers of the left ventricle and the papillary muscles and trabeculae of this chamber. When coronary insufficiency involves chiefly the right ventricle, as in massive pulmonary embolism, hypoxic necrotic foci may be encountered in this ventricle.

Beck (1938) reviewed the clinical effects and pathologic changes caused by carbon monoxide poisoning. He pointed out that it is not generally recognized that, in addition to acute asphyxiation, the gas may cause disability or death from the remote effect of acute poisoning and from the chronic effect of slow but persistent poisoning. These effects result chiefly from anovemic changes induced in the myocardium, with hemorrhage and necrosis, or from coronary thrombosis. Dack and associates (1949) have presented electrocardiographic and anatomic evidence of acute coronary insufficiency caused by pulmonary embolism. They found that the left ventricle is affected ad-

versely and often to a greater extent than the right ventricle. In their series of 41 fatal cases of pulmonary embolism, they found an electrocardiographic pattern of coronary "insufficiency." Ten patients had myocardial necrosis or infarction resulting from the acute coronary insufficiency, and none of these had acute occlusion of a coronary artery. In 3 of the 10 patients, gross changes were apparent. The commonest sites of necrosis were the subendocardial layer of the left ventricle and the papillary muscles. The right ventricle was involved in only 1 case.

Master and associates (1950) demonstrated subendocardial lesions in patients suffering from evidences of acute coronary insufficiency following acute hemorrhage, particularly of the gastrointestinal tract. As in the lesions described by Buchner (1939), the subendocardial layers of the posterior wall, septum and papillary muscles of the left ventricle contained focal or grossly recognizable confluent areas of myocardial necrosis. The necrotic muscle had a uniform appearance with loss of striations, changes in staining ability and loss of nuclei, together with scattered hemorrhages and reactive cellular infiltrations. The lesions were more severe in patients in whom the myocardial ischemia was protracted and in those with previous cardiac disease, such as severe coronary sclerosis, cardiac hypertrophy or aortic valvular disease. Inasmuch as the condition may be induced by such causes as carbon monoxide poisoning or anemia, in which there is insufficiency of oxygen supplied to the myocardium and no disease of the coronary arteries, Scherf and Golbye (1954) have proposed that the term be limited to indicate a certain pathophysiologic state and not a definite disease entity. Highman and Altland (1949) exposed rats to an altitude of 25,000 feet for 4 hours daily, none of the animals living more than one-half their normal life span. Nearly all the animals had severe vascular engorgement. Most of them had hypertrophy of the heart and thickening of the cardiac valves. Many had vegetations (usually sterile) of the valves, particularly of the mitral valve, subendocardial fibrosis of the left ventricle and fatty and other degenerative changes of the myocardium. One rat had thrombotic coronary occlusions and extensive myocardial infarction. These changes apparently are the result of repeated episodes of hypoxemia, and of secondary polycythemia.

Causes of Coronary Occlusion. The principal cause of coronary occlusion is athero-

sclerosis with or without superimposed thrombosis. The ostium of either main coronary artery may be occluded by syphilitic arteritis as an extension of the disease from the aorta. Occasionally a coronary artery may be occluded by an embolus, polyarteritis nodosa, thromboangiitis obliterans, rheumatic infection, mycotic infection, or as a result of trauma. These subjects are discussed in some detail in other sections. Occlusion may also be caused by pressure from without, as by neoplasm, extension of a dissecting aneurysm of the aorta (Bayley and Monte, 1943) or aneurysm of the sinus of Valsalva (Clippis, 1941).

Sudden Death following Administration of Drugs. Mills and associates (1949) reported 4 instances of severe myocardial ischemia, with 3 deaths, following injection of Pitressin as a diagnostic aid in cholecystography. The injection of the drug, a powerful coronary vasoconstrictor, was believed to have been responsible. McNerney and Leedham (1950) reported the occurrence of clinical acute myocardial infarction following intravenous injection of 0.5 mg. (1 ml.) ergotamine tartrate (Cynergen).

In a 52-year-old woman who died apparently of acute cardiac failure, following the subcutaneous injection of four ampules (one daily for 4 successive days) of 0.5 ml. of 1:2000 (0.25 mg.) ergotamine tartrate (Cynergen), the small coronary arteries (Figure VIII-13) showed apparent thickening of the walls and severe reduction of the lumen (Gould *et al.*, 1936). The main coronary arteries also appeared to be narrowed but no myocardial changes were observed.

Occlusion following Hemorrhage in Atherosclerotic Coronary Arteries. Paterson (1936) and Wartman (1938) have described occlusion following bleeding in the intimal lesions of atherosclerotic coronary arteries. According to Paterson, intimal capillaries often arise directly from the lumen (rather than from the vasa vasorum) of the coronary arteries in association with atherosclerosis. He believes that the intimal capillaries rupture, with resulting hemorrhage in the intima, because of (a) softening, by the atheroma, of the tissues surrounding and supporting the

capillary wall, and (b) high intracapillary blood pressure. Damage to the endothelium by extravasation of blood then leads to coronary thrombosis (Figure VIII-14). Paterson states that the intimal capillaries, arising directly from the lumen, are constantly exposed to the relatively high blood pressure within the coronary lumen; and that they are thus subject to sudden increases in coronary blood pressure. For this reason, excessive exercise and emotional stress are intimately concerned with intimal capillary rupture and, therefore, may be factors in the production of coronary thrombosis. In a study of multiple or serial sections, Paterson (1938) found such hemorrhagic foci at the site of thrombotic occlusion in 31 of 36 consecutive cases of thrombosis. He claims that high blood pressure within the coronary lumen is a factor in the production of internal hemorrhage in the vessel wall and submits evidence to show that such hemorrhages are more frequent in hypertensive than in nonhypertensive subjects.

Wartman (1938) encountered hemorrhage, usually massive, in the intimal lesions, which caused stenosis of the lumen of the affected artery. The occlusion of the coronary artery was caused solely by the intramural hematoma in 15 per cent of 41 instances; in 34 per cent of the others, intramural hemorrhage and thrombus were associated (Figures VIII-15 and VIII-16). It seemed probable that the thrombus had been formed as a result of hemorrhage following rupture of capillaries. In a subsequent report, Wartman (1949) estimated that in about 60 per cent of cases of coronary occlusion, hemorrhage into the intima is the precipitating factor. In approximately 10 per cent, occlusion is caused by an expanding hematoma; in about 20 per cent the hemorrhage is not large enough to obstruct the lumen completely, but a thrombus may be asso-



Figure VIII-14. Hemorrhage in wall of atherosclerotic right coronary artery, leading to thrombosis. (WCCII, 47 P 279A.)



Figure VIII-15. Hemorrhage in sclerotic intima of coronary artery with rupture into lumen of vessel. X 100. (WCGH, 40 A 91.)

ciated, and in more than 30 per cent occlusion is caused by rupture of the hematoma through the intima with subsequent thrombosis. Wartman (1950) has also described similar thrombosis following intramural bleeding in atherosclerotic iliac and femoral arteries.

If only one or two sections are taken from each of the main coronary arteries, hemorrhage in atherosclerotic plaques is encountered less often. Thus, French and Dock (1944) found hemorrhages in the atherosclerotic plaques of the coronaries of only 5 of 80 soldiers (6 per cent) with fatal coronary sclerosis, and Yater and associates (1948c) encountered hemorrhage in atherosclerotic plaques in 12 per cent of persons who died suddenly from coronary artery disease.

In the normal artery, only the adventitia and the outer two-thirds of the media are supplied with capillaries from the adventitial vasa vasorum; the normal intima is avascular (Ramsey, 1936-37). The ingrowth of blood capillaries about atherosclerotic plaques in the coronary arteries usually comes from the vasa vasorum and only occasionally from the intima (Wolkoff, 1929; Ehrlich *et al.*, 1931; Leary, 1938). According to Drury (1951), capillary bleeding is less important but more common from the deep transmural capillaries than from those that communicate with the lumen. Winternitz and associates (1937, 1938) have advanced the idea that hemorrhage from the capillaries in the walls of the aorta or coronary arteries is an important factor in the production of atherosclerosis.

Kowalezykova (1934) reported the occurrence, in a man aged 80, of spontaneous rupture

of an atherosclerotic branch of the left circumflex coronary artery; this led to a subepicardial hematoma and to secondary and fatal hemorrhage into the pericardial sac. Drury (1954) studied, by means of serial and step sections, the hearts of 55 persons who died from coronary disease. Each of the 55 diseased hearts had one or more occlusions; in 37 (60 per cent) the occlusions were associated with intimal hemorrhage; in 26 occlusions, there was intraluminal thrombosis and 16 of these were associated with intimal hemorrhage. The commonest cause of coronary thrombosis and intimal hemorrhage, either separately or combined, was destruction of the endothelium by the atheroma. He found no evidence that hemorrhage is important as a precipitating cause of coronary thrombosis.

Fatal Coronary Occlusion without Infarction. Blumgart and associates (1941a) explained the occurrence of complete coronary occlusion or severe narrowing of one or more coronary arteries without evidence of myocardial infarction, by the slow progress of the obstructing lesion which allows sufficient time for the formation of an adequate collateral coronary circulation. In the hearts of approximately two-thirds of 177 patients who had had angina pectoris during life, Blumgart and associates (1950) found at least one old complete occlusion of a main coronary artery or of a primary branch. Karsner (1935) states that he has not observed infarction to result from gradual occlusion of the coronary arteries by arteriosclerosis. It is believed that, in a significant number of cases of coronary artery disease, *myocardial ischemia* rather than true myocardial infarction, may result in cardiac standstill or an abnormal rhythm, such as ventricular fibrillation, and be responsible for death (York and Bell, 1946; Edwards, 1957).

Holzyke (1945), by injection of the coronary arteries by Schlesinger's method, found old occlusions in 11 hearts, in 3 of which no old infarcts were present; he also encountered 5 hearts with recent occlusions, 2 of which showed no recent infarction. Ravin and Geever (1946) demonstrated coronary occlusion in 18 injected hearts; in 5 of these 18, infarction was absent. In approximately three-fourths of cases of sudden death from coronary "insufficiency" (see page

562, Yater *et al.*, 1948c), no gross myocardial infarction was found. In most of these cases, the coronary arteries showed sclerotic occlusion without thrombosis, a lesser number, sclerotic occlusion and thrombosis, and a small percentage, neither sclerotic occlusion nor thrombosis. When sudden death occurs from a *rapidly forming thrombus* at the site of an atherosclerotic plaque, before myocardial necrosis appears, the heart usually shows evidence of previous damage (Monckeberg, 1924). The development of thrombosis of an atherosclerotic vessel further reduces

the capacity of the coronary artery to nourish the myocardium adequately and thus increases the chance of death from acute insufficiency.

Morris (1951) listed the following three main interacting elements in ischemic heart disease: (1) atheroma, with narrowing of coronaries, vascularization of intima, necrosis and hemorrhage; (2) recent and old occlusion of the coronaries; and (3) collateral circulation.

MYOCARDIAL INFARCTION

Etiologic Considerations

Myocardial Infarction in Infancy. Ravich and Rosenblatt (1947) found no reported cases of myocardial infarction in the newborn and only 4 in infancy. They studied myocardial infarction in 2 newborn infants, one aged 10½ hours and one, 2 days. In the first case there were thrombi in the coronary arteries and veins and an infarct in the dorsal wall of the left ventricle. The thrombosis was related to trauma incident to birth. In the second case, branches of the coronary arteries showed medial sclerosis and thrombosis.

Ellis (1935) encountered in a 9-month-old hydrocephalic infant, aneurysmal formations at and above the apex of the left ventricle, occurring within an area of infarction. Jokl and Greenstein (1944) described fatal coronary sclerosis in a boy of 10 years who died 5 minutes after a boxing match. The descending branch of the left coronary was obstructed by a thrombus one inch long, beginning one-half inch from the orifice. Above and below the occlusion, there were atheromatous changes in the intima. Histologically, the vessel was almost completely occluded. The intima was considerably thickened and hyalinized. There were several plaques of calcium between the intima and media and the surrounding tissues were infiltrated with erythrocytes. The internal elastic layer was disrupted and completely absent in parts.

Severe coronary atherosclerosis with occlusion and myocardial infarction may also be seen in early childhood in familial hypercholesterolemia and xanthomatosis (see pages 572 and 573), and in infancy when either or both coronary arteries arise from the pulmonary trunk. (See page 427.)

Fatal Coronary Occlusion or Myocardial Infarction Before Age 40. Underdahl and Smith (1947) found reports of only 27 women with clinical coronary artery disease among 95,000 women under 40 who were seen at the Mayo Clinic between 1935 and 1945, 7 had definite myocardial infarction and 2, questionable infarction. They believe that coronary disease in women under the age of 40 is rare except in association with obesity, hypertension or hyperlipemia. Evans and Graybiel (1948) reported fatal coronary thrombosis in a woman of 19 with hyper-



Figure VIII-16. Another segment of same section of coronary artery as that shown in Figure VIII-15, showing intramural hemorrhage and thrombosis. X 100.

tension. They believe that their patient was the youngest woman on record with fatal thrombosis. At autopsy they found occlusion of the right coronary, atherosclerotic narrowing of the left coronary, and areas of myocardial scarring. Yater and associates (1948a) reviewed the literature on coronary artery disease in persons under 40. The total number of persons reported to be under 20 years of age was 14 (9 males, 3 females, sex of 2 not stated), between 20 and 29 years, 128 (109 males, 3 females, sex of 16 not stated); under 40 years, 744 (597 males, 29 females, sex of 118 not stated). These totals include the report of Meessen (1944) of 326 German soldiers, of whom 78 were between 20 and 29 years of age.

Yater and associates (1951) compared the findings at autopsy in 450 men under 39, with those in 500 men over 40. They found that men under 40 were much more likely to have thrombotic occlusion alone than were older men, and that the latter were more likely to have either simple narrowing of the coronary arteries or both sclerotic and thrombotic occlusion. Adlersberg and Zak (1952) studied two groups of 50 persons with fatal coronary artery disease, one group ranged from 27 to 46 years of age, the other from 60 to 83 years. The younger group was characterized by an increased familial occurrence of heart disease, a shorter clinical history, relatively more men, a greater percentage of women who were overweight, a high incidence of heavy smokers (none in the older group), a lower incidence of hypertension and diabetes, and higher levels of cholesterolemia. In the younger group, there was a greater occurrence of extreme heart weights (500 Gm. or more), despite the lower incidence of hypertension, possibly because of a greater ability at compensation of the myocardium in the young. Disproportion between severe coronary disease and mild systemic atherosclerosis was often found in the younger group.

Age at Onset of Angina Pectoris and of Myocardial Infarction. As one would expect, the average age at onset of angina pectoris is lower than at onset of myocardial infarction. Riseman and Brown (1937), in 100 patients with clinically proved angina pectoris in whom symptoms were induced by a standard exercise, determined the age of onset as follows: 5 per cent in the thirties, 30 per cent in the forties, 49 per cent in the fifties and 16 per cent in the sixties. The average age at onset of infarction in 222 patients studied

by Bean (1937) was 61 years (males 60.1 years, females 61.7 years). Approximately 10 per cent of the patients were in the forties, 25 per cent in the fifties, and 35 per cent in the sixties. Chambers (1946) followed 100 consecutive patients after their initial attack of acute myocardial infarction. The ratio of men to women was 3 to 1. The women in the series were older and their mortality rate was higher than that of the men. This is true in most studies of a similar nature.

Incidence of Myocardial Infarction at Autopsy. Benson and Hunter (1925) encountered infarcts in 4.1 per cent of 1750 autopsies. Barnes and Ball (1932) of the Mayo Clinic, in a series of 1000 consecutive autopsies, found 49 hearts with old or recent infarcts (4.9 per cent). Forty of the patients were men, 9 were women. In 18 the infarct was the cause of death and in 19, a contributory cause of death. McCain and associates (1950) of Western Reserve University reviewed 3559 autopsies which were performed during the 10-year period from 1936 to 1945 inclusive. Myocardial infarcts were found in 281 persons (7.8 per cent), of whom 198 were male and 83 female. This gave an incidence of 8.7 per 100 autopsies in males and 6.5 per 100 autopsies in females, or a corrected ratio of men to women with myocardial infarcts of 1.3:1. The average age at death for men was 60.9 years, for women, 62.9 years; for Negroes, 56.1 years and for white persons, 62.2 years. Among 149 patients it was possible to determine the date of occurrence of the infarction and in 95 of these, death occurred within 1 month after onset. Gould and Cawley (1958), in a series of 5000 consecutive autopsies, encountered 588 hearts with old or recent infarcts (11.76 per cent). The average age of the 588 patients was 68.2 years. If we combine these four series, we have a total of 990 hearts with infarcts among 11,309 autopsies, or an incidence of 8.75 per cent.

Master and associates (1939c) estimated the number of attacks of coronary occlusion that occur annually at 1,000,000 while Friedberg (1949) placed this number at about 500,000. If we assume that the average in-

cidence of 8.75 per cent of myocardial infarcts found in the above-mentioned 4 series of autopsies is representative for the United States, then among the total number of over 1,500,000 deaths annually in the United States, myocardial infarcts will be found in approximately 130,000 persons at autopsy; and if the average length of life following the first attack of myocardial infarction is taken as 5 years (Katz *et al.*, 1949), then there are now approximately 650,000 persons living in the United States who have had one or more infarcts.

Rintelen (1932) of the Basle Pathological Institute found, among 5200 autopsies, fresh myocardial infarcts which he regarded as the cause of death in 51 instances (1 per cent). Gould and Cawley encountered 136 hearts (2.7 per cent) with fresh or recent infarcts (see below).

Undiagnosed Myocardial Infarctions. Aspenström (1954), in a pathologic study, found among 138 recent infarctions that 27 (20 per cent) were undiagnosed, and among 59 old infarctions that 47 (80 per cent) were not recognized. The main causes of missed diagnoses seem to have been the absence of classic pain and of electrocardiographic signs. Painless infarcts occurred chiefly in old patients and in those with cerebral damage or diabetes. Among 250 patients with gross cardiac scars indicative of healed myocardial infarctions, Edwards (1957) found that only 108 had clinical evidence of an acute infarct. In a series of 5000 consecutive autopsies in a county general hospital, Gould and Cawley (1958) found 588 hearts with one or more infarcts (11.76 per cent). Of these, 136 (2.7 per cent) were fresh or recent; 277 (5.5 per cent) were old infarcts which were diagnosed or suspected; and 175 (3.5 per cent) were old and unsuspected. Thus, of the total of 452 old infarcts, 38.7 per cent were undiagnosed.

Incidence of Sudden Death from Coronary Disease. Sudden death may be defined as unexpected death, occurring within 24 hours of the onset of symptoms.

Hamman (1934) analyzed reports of series of sudden deaths by several authors and calculated that 91 per cent of 700 such deaths from

natural causes resulted from diseases of the cardiovascular system and 40 per cent of all sudden deaths from natural causes resulted from disease of the coronary arteries. The most important natural causes of sudden death and their relative incidence were as follows:

Cause of Death	Per Cent
Disease of the coronary arteries, including syphilitic occlusion of ostia	40
Aneurysm of aorta	12
Valvular heart disease	12
Myocardial disease	8
Cerebral hemorrhage	8
Pulmonary embolism	5
Pulmonary hemorrhage	5
All other causes	10

In a series of 500 cases of sudden cardiac death, subjected to *legal autopsy in Copenhagen*, Munck (1946) found that 79 per cent were associated with coronary sclerosis, 11 per cent with syphilitic aortitis, and 4 per cent with valvular disease, mainly aortic stenosis. Twenty per cent of those with coronary disease revealed no occlusion or myocardial infarct, 36 per cent had a thrombus and 19 per cent, a fresh infarct. Moritz and Zamcheck (1946) found, among a series of 115 cases of *sudden death of American soldiers from coronary atherosclerosis*, evidence of coronary thrombosis in 31, sclerosis without thrombosis in 23, and severe sclerosis without thrombosis or obliteration in 61. In 22 hearts, infarcts were present, 13 of these were recent and 7 were old, 27 other hearts had myocardial fibrosis but no myocardial infarct was recognized. (See also Cardiac Lesions in Sudden Death from Coronary Disease, page 599.) In a series of 2030 cases of sudden and unexpected natural death in New York City, Rabson and Helsen (1948) determined that in 45 per cent of cases death was attributable to diseases of the heart and aorta, and in 30 per cent to coronary sclerosis. In three-fourths of the deaths from coronary sclerosis, coronary occlusion was not associated with a thrombus, and in the remaining fourth, the thrombus was not always fresh.

Yater and associates (1948c), in a study of the hearts of 450 men 18 to 39 years of age who died suddenly from coronary artery disease, found only sclerotic occlusion in 39 per cent, only thrombotic occlusion in 33 per cent, both sclerotic and thrombotic occlusion in 13 per cent, and neither sclerotic nor thrombotic occlusion in 10 per cent. In only one-fourth of the 450



Figure VIII-17. Closure of ostium of high-placed right coronary artery by atherosclerotic plaque. Heart was the seat of fresh infarction (Courtesy Dr. J. L. Chason and Jerome Schleifer, Veterans Administration Hospital, Dearborn, Mich. WCGH, 55 P 203)

hearts was gross evidence of myocardial infarction present.

It is thus seen that heart disease is the commonest cause of sudden death from natural causes; that the commonest type of heart disease at fault is coronary atherosclerosis, and that in approximately one-half of instances of sudden fatal coronary disease, neither arterial thrombi nor fresh myocardial infarcts are present.

Sex Incidence in Myocardial Infarction. The incidence of myocardial infarction among men is at least three times that among women. Master and associates (1939b), in a study of 500 patients with myocardial infarction from coronary occlusion, found a ratio of men to women of 3.4 to 1; Baker and Willus (1938) a ratio of 7 to 1; and Chambers (1946), a ratio of 3 to 1.

Race Incidence of Coronary Thrombosis and Myocardial Infarction. Peery and Langsam (1940) reported that coronary thrombosis in the Negro, with or without hypertension, was relatively rare. Among persons over 30 years of age who died of cardiovascular disease, coronary thrombosis was responsible for death in 3.0 per cent of Negroes and in 14.6 per cent of white persons. Fitzgerald and Yater (1946) determined from the autopsy records of a Washington (D.C.) hospital that

Negroes had a tendency to die of myocardial infarction about a decade earlier in life than did white persons. Yater and associates (1951) found that, of 635 soldiers on active duty in World War II who died of coronary artery disease, 3.5 per cent were Negroes, as compared to an incidence of Negroes in the army population of 10 per cent. (See also page 571.)

Weiss and Gray (1954) presented evidence that myocardial infarction in Negroes was infrequent in the absence of hypertension. McVay and Keil (1955) found that myocardial infarction was as frequent in Negro men as in Negro women, but was three times as common in white men as in white women. The average ages of those with infarction were as follows: Negro women, 55 years; white women, 65 years; Negro men, 61.7 years, white men, 62.7 years. Among the 558 hearts with infarcts studied by Gould and Cawley (1958), the incidence of infarcts among white patients was 12.8 per cent and 6.0 per cent among Negroes. The average age of all 588 patients was 68.2 years; of white patients 68.8 years; of Negro patients 61.8 years. The average age of white women was greater than that of white men; of Negro women less than that of Negro men.

Occlusion of Anomalous Coronary Arteries. When the orifice of a coronary artery (more often the right coronary artery) is located in the wall of the aorta above its normal position (Von Glahn, 1936), it is particularly predisposed to involvement by syphilitic aortitis (Figure VII-10). When the orifice is thus situated abnormally high, it is also more likely to be occluded by an atherosclerotic plaque (Figure VIII-17).

A single coronary artery may take over the function of the absent vessel, without damage to the myocardium, and appear at autopsy as an incidental finding (Krumhaar and Ehrlich, 1938). (See Chapter VI, pages 425 to 428.) Roberts and Loube (1947) reviewed 31 cases of congenital single coronary artery (single right artery, 17; single left artery, 11; identity of artery undetermined, 3). The average was 39 years; 4 of the patients were less than 10 years old, 14 over 40 years of age. Absence of the left coronary artery (the single artery being the right coronary artery) was

associated in 4 patients with myocardial infarction, and in 3 patients with myocardial fibrosis or ischemia. This indicates that the right coronary artery alone is less able to maintain an adequate blood supply to the heart than is the left artery alone.

Either coronary artery or both *coronary arteries may arise from the pulmonary trunk*. Origin of the right coronary from the pulmonary is rare, having been reported twice (Mönckeberg, Schley, consult Kaunitz, 1947), both times in adults. In these cases both coronaries were dilated, the right one being thin-walled and resembling a vein. Kaunitz reviewed 27 cases, 20 in infants aged 2½ to 13 months and 7 in adults aged 17 to 64 years, in which the left coronary took its origin from the pulmonary trunk. In such cases there is chronic anoxia of the portions of the heart supplied by the left coronary, with shrinkage, fibrosis, and calcification of the left anterior papillary muscle. If the collateral circulation is inadequate between the coronary arteries or between the left coronary and the left ventricular cavity, the left ventricle may show dilatation and hypertrophy and even aneurysmal bulging, fibroelastic thickening of the endocardium, focal areas of calcification and dilated sinuses in the myocardium, while the left coronary artery is wider and thinner than normal, its media showing a poorly developed muscular layer and its intima having fibroelastic thickening.

Only 2 cases have been reported in which both coronaries arose from the pulmonary trunk; in each of these, life was maintained for only 10 hours (Grayzel and Tennant, 1934; Limbourg, 1937). The cardiac hypertrophy that occurs as a result of anoxia when the left coronary arises from the pulmonary trunk is regarded as strong evidence that chronic coronary insufficiency can cause cardiac hypertrophy.

Dutra (1950) reported, in a 5-month-old male infant, origin of the left coronary artery from the first portion of the right pulmonary artery. The branches of the left coronary artery showed thickening of the intima while the left ventricle showed subendocardial fibrosis and two recent infarcts, together with

fibrosis and calcification of the myocardium. One of the 3 cases of origin of left coronary artery from the pulmonary trunk, reported by McKinley and associates (1951), was unique in that the 2-month-old male infant died from hemopericardium following rupture of the infarcted myocardium.

Coronary Occlusion in Dextrocardia. Clinical coronary occlusion has been reported (Crawford and Warren, 1938) in a patient with situs inversus and congenital dextrocardia. The patient had pain localized in the right side of the chest and numbness in the right arm.

Factors in Causation of Myocardial Infarction. Myocardial infarction is the result of sustained, relatively severe myocardial ischemia. In most cases the ischemia is caused by coronary occlusion; this may be sudden, as in embolism; relatively sudden, as in thrombosis, especially when thrombosis results from hemorrhage into the wall or into the lumen of the vessel; or gradual, as in coronary atherosclerosis without thrombosis. Gross (1921) listed the following *determining factors* in the production of myocardial infarcts: (a) size of obliterated vessel; (b) location of obliterated vessel; (c) duration and rapidity of obliteration; (d) condition of general circulation and of the heart musculature; and (e) age of the individual. He regarded the age of the individual affected as of prime importance, since the older the person, the greater and freer are the anastomoses and the better will he be able to withstand the effects of sudden obliteration of a nutrient vessel. In appraising the condition of the heart musculature, one must consider the presence of concomitant disease in other branches of the coronary arteries and the presence and degree of cardiac hypertrophy. Miller (1939) pointed out that possible contributory factors in myocardial infarction include those which increase the volume, viscosity, formed cellular elements, minerals or protein of the blood and those which lessen coronary flow.

Diminution of coronary flow follows (1) lowering of diastolic blood pressure, (2) decrease in systolic output, and (3) constriction of coronary arteries (Luten, 1931).

In *polycythemia vera*, the viscosity of the blood is increased, the blood stream is slowed and the tendency to arterial thrombosis, including coronary thrombosis, is increased, particularly if atherosclerosis is associated (Boas and Boas, 1949). In 33 of 98 patients (34 per cent) with *polycythemia vera* seen at the Mayo Clinic (Norman and Allen, 1937) vascular complications were present; 5 of these 33 patients had disease of the coronary arteries. Miller (1939) reported 7 cases of *polycythemia vera* which came to autopsy; of these, 3 had myocardial changes with coronary occlusions, 2 myocardial changes but no coronary occlusion, and 2 neither myocardial changes nor coronary occlusion. Vascular complications occurred in 23 of 63 patients with proved *polycythemia vera* seen at the Ochsner Clinic in New Orleans by Burris and Arrow-smith (1953). Only 3 of these patients had myocardial infarction.

Among precipitating factors in acute myocardial infarction, Bean (1937) includes exposure to very low temperatures, infections, spontaneous and insulin hypoglycemia, indirect trauma, operative trauma, anesthesia, hemorrhage, and shock. Occupation and activity did not seem to be important factors. Blumgart and associates (1941b) stressed the danger of shock in elderly patients, particularly in those with evidence of coronary atherosclerosis. In such patients shock may induce not only single, but often multiple, fresh infarction. Boas (1942) believed that, in the presence of diseased coronary arteries, the commonest external factors precipitating myocardial infarction are effort, emotion, exposure to cold, and overeating. Other factors which may induce angina pectoris or myocardial infarction, included hypersensitivity to drugs (penicillin, Pfister and Plice, 1950; acetylsalicylic acid, Perchuk, 1952), serum sickness induced by injection of tetanus antitoxin (McManus and Lawlor, 1950, Bengtsson and Pejine, 1952), infectious disease, operation and hemorrhage, insulin shock and hypoglycemia, and exposure to high altitudes, excessive heat or humidity. It is questionable if traumatic injury to the chest can initiate coronary occlusion. The cardiac damage usu-

ally induced by traumatic injury is in the nature of cardiac contusion (see page 852), although rare instances of traumatic coronary thrombosis with myocardial infarction have been reported (see page 855).

Borst and Holleman (1948) cautioned against the danger of acute coronary "insufficiency" or myocardial infarction from the rapid intravenous administration of sodium chloride to patients with latent coronary insufficiency or congestive heart failure. Bean (1937) found that approximately one-third of patients with myocardial infarction had a previous history of angina pectoris. In reviewing the work of other authors, he found preceding hypertension in 34 per cent of a total of 751 cases of myocardial infarction. Among 270 of the patients in his own series, one-half had a systolic pressure over 160 mm. mercury and a diastolic pressure over 100 before the infarction. It may be conservatively stated that approximately one-half of all patients with myocardial infarcts have or have had hypertension and cardiac hypertrophy. There is a sharp difference of opinion concerning the relationship of effort and emotion to the onset of acute coronary occlusion and myocardial infarction. Paterson (1939, 1940) stated that rupture of intimal capillaries, which may lead to coronary thrombosis, may in part be induced by the arterial pressure, and therefore recommended that all patients with coronary disease be advised to avoid excessive exertion or emotion or any other activity which may unduly raise their systemic pressure.

Blumgart and associates (1941) produced massive infarction in dogs by obstructing the blood supply to the heart for 40 minutes or longer. They believed that in man myocardial infarction may occur: (1) after sudden occlusion of a vessel which was previously adequate, if sufficient collateral anastomoses have not yet developed, and (2) without occlusion of a vessel, if the myocardial anoxemia is sufficiently prolonged. In some patients whose myocardium suffers temporary ischemia because of occlusion or narrowing of the coronaries, infarction is favored by increased demands upon the heart, as by continuation of physical effort.

Yater and associates (1948a), in their analysis of 866 clinical cases of acute coronary artery disease in American soldiers under the age of 40, including 450 who came to autopsy, found that the number of attacks occurring at the time of strenuous activity was more than twice the proportion of time spent in such activity, while the

number of attacks occurring during sleep was about one-third the proportion of time spent in sleep. They concluded that in certain cases, a thrombus or infarct may have been forming silently for some time and the type of activity at the onset of symptoms was purely coincidental, while in other cases, activity, especially if strenuous, may have caused the additional demand for coronary blood flow that precipitated the fatal attack. Of these 450 soldiers, 83 per cent died within 24 hours; 75 per cent had no infarction. In general, the longer a man lived following the onset of the attack of coronary disease, the more likely was infarction to be present at autopsy. Patients with a previous cardiac history tended to have infarcts or myocardial scars more often than those without such a history. However, Master and Jaffe (1952) believe that strenuous physical exertion is not related to the initiation of acute coronary occlusion. In 2080 patients with coronary occlusion, they found only about 2 per cent of occlusions related to strenuous activity, while in 98 per cent, the patient was at rest, asleep, or engaged in some usual routine. In contrast to Paterson's views, they believe that intimal hemorrhage is entirely a degenerative phenomenon, an end-result of atherosclerosis which occurs independently of external factors. This view is supported by the work of Winternitz and co-workers (1938) who injected dye into atherosclerotic coronary arteries at pressures up to 1000 mm. of mercury without producing rupture of intimal capillaries. It is thus seen that the relationship of effort and emotion to the initiation of acute coronary occlusion (acute coronary thrombosis or hemorrhage beneath an atherosclerotic plaque) has not yet been determined. With regard to the initiation of acute myocardial infarction, however, it appears likely that any factor which will substantially increase the work demanded of the heart of patients having significant coronary atherosclerosis can cause infarction, even in the absence of complete occlusion of a coronary artery.

Myocardial Infarction and Rate of Development of Coronary Occlusion. Clinicopathologic and experimental studies have shown that if the occlusion of a main branch is sudden, the area of infarction is large but if the occlusion develops slowly, there may be little or no necrosis. When the obstruction is gradual, anastomotic vessels develop and the heart is better able to withstand the ef-

fects of the occlusion. Most cases of sudden closure of the anterior descending vessel result from embolism of a thrombus or vegetation in the left ventricle or on the root of the aorta, in a previously damaged heart. Monckeberg (1924) stated that a person may survive sudden closure of the right coronary artery, but that he may survive sudden closure of the anterior descending branch of the left coronary only if there are many pre-existing anastomoses, the other coronary arteries are relatively free of disease, and the cardiac reserve is good. Myocardial infarction is associated with occlusion of at least two branches of the coronary arteries supplying the infarcted area (Saphir *et al.*, 1935).

Schlesinger (1938) found an infarct which resulted from rapid occlusion of a major branch, although all other branches were normal (Case 19), in 4 of 6 hearts examined, he found two occlusions. Smith and Hinshaw (1937) reported severe progressive angina pectoris in a patient aged 31, following recovery from myocardial infarction.

Infarction "at a Distance." When a branch of one coronary artery becomes obstructed, the portion of the myocardium which is rendered ischemic may then derive its nourishment principally from a branch of the other coronary artery, by development of anastomotic channels. If now the latter artery should become occluded, fresh myocardial infarction may result in the area normally and originally supplied by the first artery (Saphir *et al.*, 1935). This has been called "ectopic" infarction (Bean, 1938) or "infarction at a distance" (Blumgart, 1939). Thus, following occlusion of the anterior descending branch of the left coronary, the nourishment to the apical portion of the left ventricle may be taken over by collateral circulation from the right coronary artery; if then the right coronary artery should suddenly become occluded, the apical portion of the left ventricle may suffer acute infarction. In other words, the area of myocardium becomes infarcted owing to interruption of the blood supply furnished by the anastomosing channels of a collateral vessel.

Relation of Coronary Sclerosis to Disturbances in Conduction (see Chapter IV). Monckeberg (1924) pointed out that in infarction of the myocardium, the atrioventric-

ular conduction bundle may be involved or spared, depending upon whether the independent blood supply to the bundle is involved.

Master and associates (1938) found that defective intraventricular conduction in coronary occlusion aggravates the prognosis; the mortality rate in such cases in their series was 42 per cent as compared to a rate of 23 per cent in patients with normal conduction. In 20 hearts, studied at autopsy, of persons who had had evidence of complete or partial heart block during life, recent occlusion was present in the left coronary artery in 7, in the right in 5, and in both arteries in the remaining 8. In addition, one or more arteries had been previously occluded in 16 of the 20 hearts. In four-fifths of cases of bundle-branch block, they found infarction of the ventricular septum. They attributed such heart block to septal infarction with simultaneous involvement of the atrioventricular conduction tissues and the bundle-branch system. They also found intraventricular conduction had been present during life twice as often in patients whose hearts at autopsy showed gross septal infarction as in those in whom infarction did not involve the septum.

It may be mentioned that the right bundle branch is supplied almost exclusively by the septal branch (see Gross, 1921) of the left anterior descending artery, while the left bundle branch is supplied by branches from both coronary arteries. Master and associates found that occlusion of the right coronary artery led to bundle-branch block of either type more often than was to be expected; and they could not correlate the type of conduction defect with the vessel occluded or the location of the infarct. They explained persistence of normal conduction in association with septal infarction by the presence of adequate collateral circulation in the septum, and attributed transient bundle-branch block to temporary anoxemia.

Yater (1938) reviewed the literature on pathogenesis of bundle-branch block and reported the detailed histopathologic findings in 6 hearts in which serial sections were made through the conduction system. In each heart there was fibrosis involving both right and left bundle branches. These lesions were related to disease of the coronary arteries, rheumatic, atherosclerotic or hypertensive. Yater determined that the newer (American) terminology of bundle-branch block is more clearly correct than the old one;

that the designation indicates which branch is more seriously damaged; and that the right bundle branch is probably more often damaged as a result of rheumatic arteritis or myocarditis, while the left is usually affected by atherosclerosis or hypertension or both. Rasmussen and Moe (1948) found left bundle-branch block associated with hypertrophy of the left ventricle 5 times as often as with a local lesion of the left branch of the bundle. In their review of the literature on intraventricular block, Rosenman and associates (1950) could not correlate the histologic with the clinical findings. When blocking lesions were present, they were usually bilateral.

Diagnostic Laboratory Tests. Aside from fever and electrocardiographic evidence, the following laboratory tests are of value in the diagnosis of myocardial infarction: leukocyte count, blood sedimentation rate, C-reactive protein, concentration of enzymes and metalloenzymes in serum, and plasma fibrinogen.

Fever, leukocytosis and increased sedimentation rate. In myocardial infarction, fever, leukocytosis and increase in the sedimentation rate of blood cells are almost always present, singly or in combination, beginning during the first 24 hours.

Rabinowitz and associates (1931) found that fever and leukocytosis usually appear earlier than increase in sedimentation rate but that the increased sedimentation rate persists longer. In several of their patients on whom these tests were made on the day following the onset of the attack, the sedimentation rate was normal, but fever and leukocytosis were already present. In an analysis of temperature response in 100 patients with acute myocardial infarction, Tarnower and associates (1958) found that, after a latent period of 12 to 36 hours, 92 patients developed fever which lasted from 2 to 7 days. The peak temperature almost always appeared within 4 days of onset. They thought that the latent period, duration and peak of fever coincide well with the established histopathology of myocardial infarction. They related the fever to myocardial necrosis, which usually is not found until about 6 hours after the onset of the attack and is most marked from the second to fourth day, *i.e.*, at the time when the elevation of temperature is highest. A rectal temperature over 103° F. and late occurrence of peak temperatures were

thought to be poor prognostic signs. Fever may not be detected unless the temperature is taken rectally. The average leukocyte count is 12,000 to 15,000 and counts of over 30,000 are rare. An unusually high leukocyte count and the finding of over 30 per cent of nonfilamented polymorphonuclears after the fourth day are regarded as unfavorable signs (Goodrich and Smith, 1936). Koenig and Young (1947) have pointed out the importance of following a series of daily determinations of the sedimentation time during the first days following infarction. The most rapid increase in sedimentation time occurs 4 or 5 days after the onset of the attack. The rate may not return to normal for several weeks or several months.

Increase in serum mucoprotein following myocardial infarction. An increase in the level of serum mucoprotein after infarction was consistently found by Simkin and associates (1949). In 23 patients with recent infarction, increases of from 22 to 160 mg. above their previous normal ranges (40 to 90 mg. per 100 ml.) were noted, beginning on the third day and usually reaching a peak on the sixth day. This level was maintained for another week, after which it declined. The mucoprotein was not specific for breakdown of cardiac protein, since elevations in its value were obtained in patients after operations, and in those with cancer and pneumonia. No relation was found between the level of the mucoprotein and the sedimentation rate. It was believed that the changes in serum mucoprotein are a more accurate indication of the presence or absence of a recent myocardial infarction than are the sedimentation rate and the leukocytic count.

Glutamic oxalacetic transaminase in serum. Glutamic oxalacetic transaminase is present in certain tissues of the body, but in highest concentration in heart muscle. Normally the concentration of the enzyme in the serum ranges from 10 to 40 units per ml. per minute. In necrosis of tissue, and particularly in fresh acute myocardial infarction, its concentration in the serum is strikingly elevated. Optimally the serum should be tested 6 to 24 hours after onset of infarction. By the sixth day after onset of infarction, the concentration has usually returned to normal (Chinsky *et al.*, 1956). Values over 200 units usually indicate a poor

prognosis. The test may be of considerable value in suspected cardiac infarction in patients in whom clinical or electrocardiographic evidence of infarction is not clear-cut (Biorck and Hanson, 1956).

Other Diagnostic Tests. According to Hirshfield and Krainin (1958), the test for *C-reactive protein* becomes positive earlier than does the blood sedimentation rate and reverts to normal with the end of the acute phase at which time the blood sedimentation rate is still high; the level of serum glutamic oxalacetic transaminase becomes elevated early and returns to normal within 4 to 6 days, the levels of serum lactic dehydrogenase and malic dehydrogenase rise within 24 hours, become maximum on the second or third day and revert to normal within 7 to 11 days, the level of plasma zinc falls concomitantly with rise in lactic dehydrogenase and returns to normal within 2 weeks, while the value of serum copper rises markedly in 5 to 11 days and gradually returns to normal in 3 to 4 weeks; the concentration of fibrinogen increases early and persists for as long as 5 to 6 weeks. The prothrombin time is, of course, important in controlling use of anticoagulants in therapy.

Multiple Attacks of Infarction (Figures VIII-39 and 42). Fcil and associates (1938) found multiple acute infarcts without previous infarction in 8 of 34 patients who died of recent infarction. Master and associates (1937)

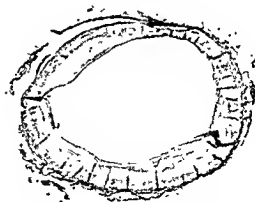


Figure VIII-18. Moderately severe atherosclerosis in proximal portion of a greatly dilated main coronary artery of a 67-year-old man. The dilatation is the result of aging. X 6½. (WCGII, 59 P 10.)

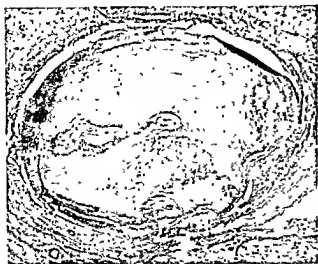


Figure VIII-19. Nearly complete old coronary sclerotic occlusion with calcification and partial recanalization. X 15. (WCGH, 55 P 191.)

obtained a history of previous coronary occlusions in approximately 50 per cent of their patients. Eleven per cent of their patients died in the initial attack, 29 per cent in the second attack and 50 per cent in the third attack.

Yater and associates (1948c) noted that, in 14 of 114 soldiers who died suddenly of coronary artery disease, the heart had two infarcts and in 2, three infarcts. Wartman and Hellerstein (1948) found a total of 235 myocardial infarcts in 160 patients. 196 (83 per cent) in the left ventricle, 22 in the right ventricle, 15 in the right atrium; and 2 in the left atrium. The left ventricle was involved in 152 of the 160 hearts. Among 94 hearts with single infarcts, the process was recent in 50 and old in 44, among 66 hearts with multiple infarcts, the lesions were recent in 10, old in 5, and both recent and old in 51.

Pathologic Considerations

Pathologic Basis of Myocardial Infarction. In most instances myocardial infarction is the result of occlusion of one or more coronary arteries. The commonest lesion is coronary atherosclerosis with occlusion or severe narrowing (Figures VIII-18, 19 and 20) at one or more locations. Frequently a fresh or recent thrombus is either superimposed on the atheromatous lesion or develops just proximal to it. Occlusion may also be caused by syphilitic involvement of the coronary orifice, although infarction seldom results from this slowly developing process. Sudden coronary

occlusion, such as caused by embolism or trauma or compression, or rupture of a coronary artery as by trauma or perforation of an aneurysm, is more likely to result in myocardial infarction. Occlusion from thrombosis occasionally occurs in rheumatic arteritis and rarely in thromboangiitis obliterans or polyarteritis nodosa.

Coronary Thrombosis. In practically every case, thrombosis of the coronary artery develops on the basis of preexisting atherosclerosis. In 46 hearts with myocardial infarcts, Levine and Brown (1929) encountered coronary thrombosis 23 times, each time on the basis of atherosclerosis; in 34 hearts with advanced coronary sclerosis, Saphir and associates (1935) demonstrated thrombi in 32, the thrombus in each instance being located on an atheromatous ulcer. The initiation of thrombosis by intimal hemorrhage in atherosclerotic plaques is discussed on page 585.

Instances of *traumatic coronary thrombosis* with fresh myocardial infarction are cited by Monckeberg (1924). Beau (1937) encountered 3 instances of traumatic myocardial infarction among 9629 consecutive autopsies. One of these concerned a patient who fell 8 feet from a ladder, sustaining fractures of the ribs of the left side. He died 10 weeks later and at autopsy a recent infarct with beginning aneurysm formation was present. H. Levy (1949) reported an example of traumatic coronary thrombosis with a myocardial infarct in a woman of 49 who had sustained a contusion of the chest wall in an automobile accident and died 13 days later. Autopsy revealed hemorrhage beneath the intima, rupture of the intimal lining and thrombosis in the lumen of the anterior descending branch of the left coronary artery, together with a large myocardial infarct involving the ventral half of the entire apex. The microscopic appearances of the thrombus and the infarct were consistent with changes which could occur in the interval between the accident and death. Friedberg (1949) stated that in cardiac wounds the coronary arteries are commonly involved, particularly the anterior descending branch of the left coronary. In the application of nonpenetrating blunt force to the chest wall, the ventral position of the right coronary artery is said (Helfern, 1949) to render this vessel more vulnerable to injury than the left artery. (See also page 855.)

Sites of Coronary Occlusion in Relation to Location of Infarcts. The sites of predilection for formation of atherosclerosis in the coronary arteries (see page 563) are the same for the development of superimposed thrombosis or of complete occlusion of the lumen. The commonest site of occlusion is the anterior descending branch of the left coronary artery about 2 cm. from its origin. The circumflex branch of the left coronary and the main stem of the right coronary are involved much less often, each of these vessels frequently being occluded about 1 cm. from its origin.

As previously mentioned, Saphir and associates (1935) determined that, in the presence of a myocardial infarct, at least two branches of the coronary arteries supplying the infarcted area are

occluded by atherosclerosis. In their series of 32 infarcted hearts, they found no instance in which *only one* main branch was involved. In this material, when only extreme narrowing of the lumen was present, without occlusion by atherosclerosis or thrombosis, at least three main branches were affected. In Bean's (1938) series of 287 infarcted hearts, the left coronary tree was seriously involved in 84 per cent, the right coronary tree in 21 per cent. In 54 infarcts studied by Mallory and associates (1939), the infarct was located in the left ventricle 53 times (apex, 24; apex and septum, 22, base, 5; base and septum, 2) and in the right ventricle, once.

Schlesinger (1938) has pointed out the consistent absence of large vessels and of fibrosis in the posterior basal portion of the right ventricle and the rarity of infarction in this location. Despite the frequency of occlusion of the right

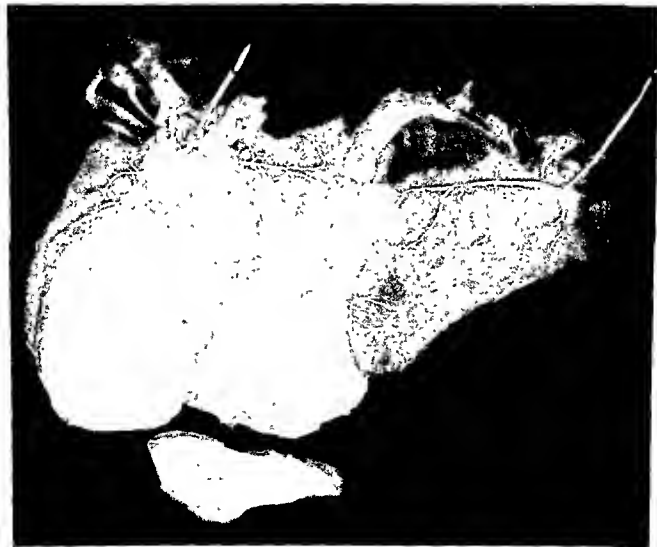


Figure VIII-20. Roentgenogram of injected heart showing segmental narrowing of coronary arteries and their branches. (Courtesy Armed Forces Institute of Pathology, Acc. 133726-254-10.)

coronary artery, infarction of the right ventricle is extremely rare because the right ventricle, like the atria, is thin-walled and may derive considerable nourishment from the blood coming directly from its cavity (Blumgart *et al.*, 1940). In a study of myocardial infarction in more than 100 hearts, Mallory and associates (1939) found definite thrombosis of a coronary artery in 70 hearts. The number of instances of thrombosis in each vessel was as follows: left coronary artery, 59 (anterior descending branch, 52; circumflex branch, 4; septal branch, 3), right coronary artery, 8, and both arteries, 3. Hochrein (1941) tabulated the sites of occlusion of the coronary arteries in 530 autopsied cases representing the total number of cases analyzed in 13 different reports in the literature. The anterior descending branch of the left coronary was occluded in 68 per cent; the right coronary artery in 21 per cent, both of these vessels in 8 per cent and the circumflex branch of the left in 6 per cent. Grewin (1948) studied the necropsy reports of 100 consecutive cases of myocardial infarction, and found complete occlusion of the left anterior descending branch in 21 cases, of the right coronary in 14 and of the left circumflex branch in 7. In the series of fatal cases of coronary artery disease reported by Yater and associates (1948c), the incidence of almost complete sclerotic occlusion (in 232 persons) affecting the various vessels was as follows: left anterior descending, 192; left circumflex, 60, right coronary, 59. The incidence of thrombotic occlusion was as follows: left anterior descending, 174; right coronary, 49; left circumflex, 28. In the vast majority of cases the occlusion, whether sclerotic or thrombotic, involved only the proximal third of the affected vessel. In 2000 consecutive autopsies, Wartman and Hellerstein (1948) encountered 235 myocardial infarcts in the hearts of 160 persons. In 94 hearts, the infarcts were single and in 66 multiple. There were 134 hearts with infarcts in the left ventricle only; 18 with infarcts in both ventricles, 4, in the right atrium only; and 4, in the right ventricle only. In a series of 137 hearts, Yater and associates (1948c) found a total of 153 myocardial infarcts (130 gross and 23 microscopic). The infarcts were located in the left ventricle and, or, the ventricular septum in all but 7 instances. These 7 infarcts were located in the posterior wall of the right ventricle. Yater and associates (1951) found, among 950 soldiers who came to autopsy with coronary artery disease, that the incidence of posterior infarcts increased with age, and that the tendency to involvement of the right

coronary artery or left circumflex artery or both increased with age.

Infarction of the Atria. Cushing and associates (1942), in a postmortem study over a period of 7 years, searched for atrial infarcts. Among 182 consecutive hearts with myocardial infarcts they found 31 with atrial infarcts (17 per cent). In 6 hearts only the atrium was involved; in the other hearts, the atrial infarcts were associated with ventricular infarcts. The right atrium was involved in 27 hearts, the left atrium in 5. Mural thrombi were associated with 26 of the 31 atrial infarcts. The clinical findings were generally not significant with regard to atrial infarction, but among the patients who had had electrocardiograms, approximately two-thirds had evidence of some abnormal atrial mechanism. Of 66 atrial infarctions reported in the literature, rupture of the atrial wall occurred in 3 (Soderstrom, 1948).

Soderstrom, who made a thorough study of atrial infarcts, stated that they are to be expected in at least 1 per cent of hearts in an average autopsy material. He collected 192 hearts with mural thrombi in the atria and microscopically examined the adjacent atrial walls for evidence of infarction. Right atrial thrombi were somewhat commoner than left atrial thrombi. In the right atrium they were commonly associated with coronary heart disease; in the left atrium they were usually associated with rheumatic heart disease. In 46 cases he encountered infarcts in the right atrium and in 1 case an infarct of the left atrium. The rarity of left atrial infarcts is attributed mainly to the high oxygen tension in the blood within the lumen of this chamber. Ventral infarcts of the right atrium usually involved the auricular appendage, while dorsal infarcts represented an extension of "posterior" infarcts of the left ventricle. Atrial infarcts were difficult to recognize both grossly and histologically. In the central zone of infarction, the necrosis is of hyaline type, similar to that commonly seen in ventricular infarcts; in the subendocardial zone, the myocardial damage is less severe, apparently because the myocardium derives some nourishment from the blood within the lumen of the chamber.

In a study of the autopsy reports of 281 persons with myocardial infarcts, McCain and associates (1950) found that the atrium was infarcted

in 24, an incidence of 8.5 per cent, in 17 of the 24, the infarct was recent. Wartman and Souders (1950), in a study of 50 hearts containing a total of 72 infarcts, found infarcts in the atria in 21 hearts (42 per cent). These were located in the right atrium in 17, in the left in 2, and in both atria in 2, and they were always associated with ventricular infarcts. Most of them were fresh. The infarcts were thought to be a contributory factor in death.

Cardiac Lesions in Sudden Death from Coronary Disease. As previously stated, in most instances of sudden death from coronary insufficiency, one or more coronary arteries are occluded; in a few cases the coronary arteries are relatively free of disease and in most of these the left ventricle is greatly hypertrophied, chiefly as a result of hypertensive disease. In most instances, the heart will reveal neither coronary thrombosis nor gross evidence of fresh infarction, but rather a severe degree of atherosclerosis at one or more points, or extensively in two or all three of the main vessels. A precipitating factor (see page 592) is often present, but sometimes inapparent or absent. If death ensues within a few hours after the onset of the acute attack of coronary insufficiency, no gross myocardial change may be evident. If death occurs after 5 or 6 hours or within a few days, the necrotic muscle may be deep red in color because of extravasation of blood, or clay-colored because of local anemia, and interspersed with or bordered by zones of red (hemorrhage) and yellow (fatty degeneration and leukocytic infiltration). After several days, with beginning organization the areas of myocardial necrosis may appear darker brown than the adjacent muscle, and soft, depressed and dry. The softness of the necrotic muscle was responsible for the old term "myomalacia cordis," introduced by Ziegler (1880).

Gross and Microscopic Changes in Experimental Infarction. Karsner and Dwyer (1916) ligated the descending ramus of the left coronary artery in dogs and sacrificed the animals at various intervals from one-half hour to 70 days. They described in detail the gross and microscopic myocardial changes. Grossly, the first recognizable change was pallor; after 2 days, the

infarct was dry and granular; after 5 days, the infarct was sharply defined and surrounded by a fine line of reactionary hyperemia, after 61 days, fibrosis was complete but minute yellow necrotic areas were still to be seen. Microscopically, the changes noted after one-half hour were congestion, edema, small hemorrhages and decrease in cross-striations of myofibrils. Cloudy swelling of muscle was seen at 1½ hours. At 12 hours, the muscle showed hyaline necrosis and the nuclei were pyknotic or had disappeared, polymorphonuclear leukocytes and a few mononuclear cells had infiltrated the area of necrosis. These changes were more pronounced at 24 hours, at which time mitotic figures were recognized in the perivascular and subendothelial connective tissue. Fatty degeneration appeared at 24 hours and remained until the necrotic muscle disappeared. Anitschkow "myocytes" also appeared at 24 hours but were infrequent after 5 days. The muscle cells occasionally showed nuclei after 24 hours; later so-called muscle giant cells were seen, apparently formed by the accumulation of nuclei. Foreign-body giant cells also appeared at the same time but persisted longer. At 48 hours, the fibroblasts had increased in number, and at 5 days they formed a well-defined zone at the periphery of the infarct. At 6 days, plasma cells were present; a few persisted up to 70 days. After 11 days, the necrotic muscle decreased in amount, being replaced by connective tissue. At 18 days, a well defined scar was present but inflammatory cells remained. After 61 days, the connective tissue was condensed, very minute areas of necrotic tissue were still present, but cellular infiltration had disappeared. No evidence was seen of true muscle regeneration.

It is probable that these changes in the dog proceed at a more rapid rate than would occur in myocardial infarction in man, since the metabolic rate in the dog is relatively greater than that of man. It has also been pointed out that the size of the infarct and the size of the heart are smaller in the dog and that the remaining collateral blood supply is better than in man because of the absence of severe atherosclerosis. Yokoyama and associates (1955) studied the histochemical changes in early myocardial ischemia in dogs. Within 1 hour after occlusion of a coronary artery, the ischemic muscle showed marked reduction in the stainable glycogen with the periodic acid-Schiff technique. At the time granulation tissue formed, some of the myocardial fibers immediately surrounding the infarct revealed increased quantities of glycogen.

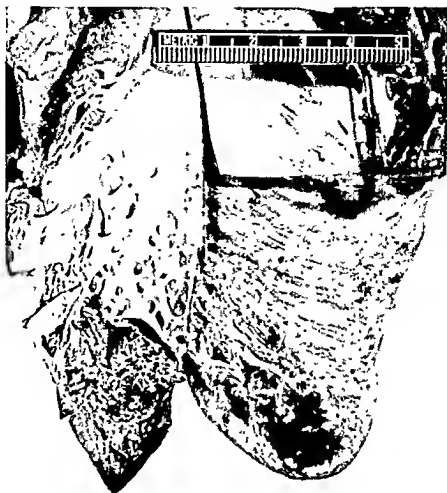


Figure VIII-21. Old and fresh myocardial infarcts. History of myocardial infarction 6 years before death, last attack, 3 days before death. (WCGH, 49 A 483)

Gross Changes in Myocardial Infarction in Man. Gross changes ordinarily do not develop for 5 or 6 hours after an acute attack. If extensive myocardial infarction is found at autopsy in a person who has died within an hour or two after the onset of an acute attack, the infarct must be related to conditions existing prior to the onset of the attack. The earliest change is a loss of lustre of the necrotic muscle. This soon becomes pale, dry and somewhat swollen. The zone between infarcted and living muscle is usually irregular. Within a day or two, the muscle assumes a clay color if the infarct is diffuse, or a streaked yellow appearance if the infarct is patchy. The yellow color is explained by fatty degeneration of the necrotic muscle fibers and, at the border of necrotic areas, by infiltration with polymorphonuclear leukocytes,

particularly within the first 5 or 6 days of the infarct. In patchy areas of infarction at this period, there may be a mixture of healthy and dead or dying muscle, fatty change from infiltrated leukocytes, and congestion or hemorrhage, with a corresponding variety of colors (Figure VIII-21). There may be considerable liquefaction necrosis with disappearance of many muscle fibers, thus accounting for much of the loss of thickness of the myocardial wall after healing of large infarcts. The border of the infarct may be red because of hyperemia of adjacent vessels or hemorrhage from extravasation of blood from these vessels; at the end of 1 week, the red color may in part be explained by young granulation tissue. After the first week or 10 days, the border becomes depressed owing to shrinkage following removal of necrotic mus-

cle. The depressed zone becomes progressively wider and paler, and the granulation tissue is replaced by fibrous tissue and after 2 or 3 months, by a white scar.

If the infarct extends to the epicardial surface, a *pericarditis* develops which usually is largely fibrinous but may have some hemorrhagic or purulent component; with survival of the patient, it heals by organization and scarring. If the infarct extends to the *endocardial surface*, a thrombus usually forms at the site. The resulting thrombus may cause narrowing of the lumen of the ventricle or the site of thrombosis may be marked by aneurysmal bulging of the ventricular wall.

In hemorrhagic areas of infarction involving a good portion of the thickness of the cardiac wall, particularly if the epicardial surface is involved, there may be *rupture of the wall* with ensuing fatal hemopericardium. In such cases, the entire thickness of the ventricular wall is usually infarcted. More often, however, infarcts undergo organization

and are replaced by gray-white scars, sometimes with a trace of pigment apparent. A patchy area of old scarring may be situated adjacent to, or be the site of, an organizing recent infarct (Figure VIII-21) or a new fresh infarct which is either patchy or diffuse in distribution. These coexisting changes may be the result of progressive narrowing of one or more branches of the coronary arteries.

Microscopic Changes in Myocardial Infarction in Man. In an admirable report, Mallory and co-workers (1939) described the microscopic changes in myocardial infarcts in the hearts of 72 persons in whom the onset of clinical findings enabled them to determine the age of the infarct. Their microscopic findings may be summarized as follows:

1. *Necrosis of muscle, connective tissue and smaller blood vessels.* Necrosis does not become evident for 5 or 6 hours; the muscle fibers then become hyaline and take a deeper acid stain, while the striations become less

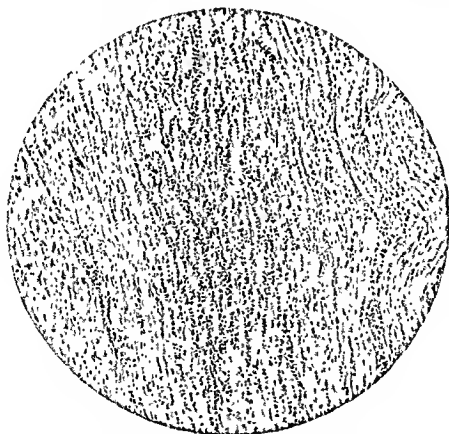


Figure VIII-22. Acute inflammation at border of recent myocardial infarct. Leukocytes are mainly polymorphonuclear. Onset of attack 2 days before death. X 150. (WCGII, 40 A 485.)

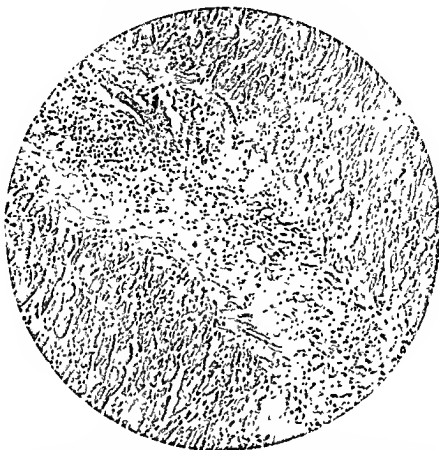


Figure VIII-23. Portion of infarcted myocardium in person whose symptoms began 8 days before death. Note partially necrotic muscle fibers, fibroblasts, young granulation tissue, and inflammatory cells (chiefly lymphocytes). X 150 (WCCB, 41 A 14.)

evident; the nuclei undergo pyknosis, karyorrhexis or karyolysis. A layer of intact muscle, 0.3 to 0.5 mm. thick, usually persists beneath the endocardium, the nourishment for these fibers apparently being provided directly by blood in the cavity of the heart and in the thebesian veins.

2. *Hemorrhage* is usually focal rather than diffuse, and extravasations are relatively rare. The venules and capillaries are hyperemic. Hemolysis of erythrocytes results in deposition of hemosiderin which is phagocytized by macrophages. The infarction has features of both hemorrhagic and anemic types.

3. *Fat* varies in amount depending on the suddenness of infarction and previous sufficiency of circulation. Most of the fat is found at the periphery of the infarct. The fat is removed by the macrophages at the same time as the necrotic muscle. As stated previously, the fatty material is derived from dead or

dying muscle fibers or from accumulation of leukocytes.

4. *Infiltration with polymorphonuclear leukocytes* (Figure VIII-22) begins at about 5 hours, at the edges of the lesion and spreads centrally. It is present in the interstitial tissue and about the blood vessels and gradually extends into the necrotic tissue. At 24 hours, the infiltration of leukocytes is slight, with beginning degeneration; at 5 days, many are necrotic; and thereafter they gradually disappear. Mallory and associates suggested that the polymorphonuclears may produce an enzyme which aids to the breakdown and phagocytosis of the muscle. *Eosinophilic polymorphonuclears* also are seen between the fourth and eighteenth days.

5. *Ingrowth of blood vessels and connective tissue.* Beginning on the fourth day new blood capillaries grow into the infarcted area, starting peripherally. Fibroblasts accompany the

blood vessels into the infarcted area (Figures VIII-23, 24, and 25). The ingrowth is relatively greater on the epicardial than on the endocardial side. If the infarct is large, the vascularization may not reach the center.

6. *Removal of necrotic muscle. Infiltration by pigmented macrophages.* Simultaneously with the ingrowth of new capillaries and fibroblasts, macrophages invade and phagocytize the necrotic tissue. Occasionally giant cells may appear (Monckeberg, 1924). The fragments of muscle dissolve and disappear but their lipofuscin remains within the macrophages which become pigmented. Some macrophages also contain hemosiderin which is produced from the breakdown of the red cells in areas of hemorrhage. After about 10 days, 1 mm. of necrotic peripheral muscle has been removed, and after 6 weeks, active absorption of necrotic muscle may still be present. At 2 months, necrotic muscle fibers have generally been completely removed. After 1

year, practically all pigmented macrophages have disappeared. According to Monckeberg, one may occasionally see an attempt at muscle regeneration adjacent to the infarct.

7. *Lymphocytes and plasma cells* appear as soon as absorption of muscle starts, are fairly prominent during the third week and disappear about the same time as the pigmented macrophages. Occasional mononuclear cells persist for many months.

8. *Collagen*, produced by the fibroblasts, appears first at 12 days, is prominent at 3 weeks and maximum at 2 to 3 months. The amount of collagen provides a good indication of the age of the infarct. At 6 weeks the scar becomes contracted. Adjacent to old infarcts, the muscular fibers are often hypertrophic and their nuclei hyperchromatic (Monckeberg, 1924).

9. *Pericarditis.* Fibrinous pericarditis (Figure VIII-26) appears within 24 hours. Organization of the exudate begins at 4 to 8 days

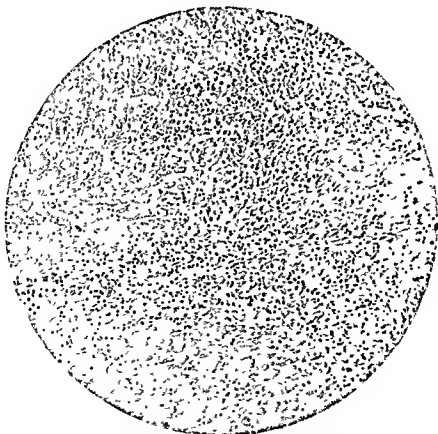


Figure VIII-24. Granulation tissue at border of myocardial infarct. Symptoms began 16 days before death. At this time collagenous fibers are present at the border of the infarct. X 150. (WCCII, 41 A 115.)

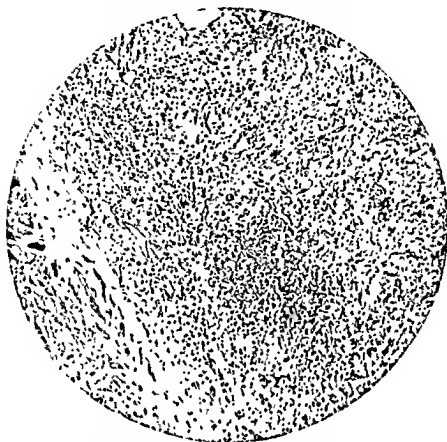


Figure VIII-25. Portion of healing myocardial infarct. History of acute attack 5 weeks before death. X 150. (WCGII, 40 A 460.)

and is complete at 4 weeks. The pericardial reaction also provides a basis for judging the age of the infarct.

10. *Endocardial thrombus.* Thrombosis begins as early as 5 days but may occur much later. It is thought by some to be the result, not of the infarct, but of secondary dilatation of the infarcted wall. Its organization begins on the ninth day and complete organization may be present on the sixteenth day. Organization of the thrombus, however, is not a reliable guide in estimating the age of the infarct. Mallory and associates pointed out that, from the microscopic picture, the age of an infarct may be judged well during the first 3 weeks; that small infarcts heal more rapidly than large ones; that subendocardial infarcts heal less rapidly than those in the center of the myocardium or beneath the epicardium; and that the rate of healing depends on the competency of the remaining circulation and, therefore, on the degree of coronary athero-

sclerosis, and on the amount of heart failure and anemia.

On the basis of their findings, Mallory and associates (1939) advised that patients with small or moderate-sized myocardial infarcts, without complications, be allowed 1 month of rest in bed, 1 month of carefully graded convalescence, and a third month to consolidate recovery.

Myocardial Infarction with Coronary Occlusion. In most instances, myocardial infarcts are associated with coronary occlusion. Plotz (1948) estimated that 90 to 95 per cent of myocardial infarcts are the result of coronary sclerosis. Approximately two-fifths are associated with thrombotic occlusion alone, two-fifths with sclerotic occlusion, and one-eighth with both sclerotic and thrombotic occlusion (Yater *et al.*, 1948c). In most cases, all three main coronary vessels are involved by the atherosclerosis.

Myocardial Infarction without Coronary

Occlusion. In Bean's series (1938) of 300 myocardial infarcts, 20 per cent were associated with arterial narrowing but no arterial thrombi. In 4 hearts the coronary arteries showed no significant damage.

Gross and Sternberg (1939) reported that in 15 hearts with extensive infarction (1 recent, 14 healed) the coronaries showed insignificant intimal changes and scant narrowing of the lumina, 13 of these were associated with hypertension. Twelve hearts weighed 350 Gm. or more and, in 8 instances, the weight ranged from 470 Gm. to 810 Gm. Among 114 hearts with gross myocardial infarcts studied by Yater and associates (1948c), 8 showed no complete occlusion of any artery. Wartman and Hellerstein (1948), in a study of 160 infarcted hearts, found neither disease nor occlusion of the coronary arteries in 3.8 per cent. Such occurrences must be explained by prolonged *relative myocardial ischemia*. In a study of 143 cases of acute infarction, Miller and associates (1951) found that in 49 patients (34 per cent), there was no recent or acute coronary occlusion. The average weight of the hearts of these 49 patients was 70 per cent over their

normal predicted weight, while the average weight of the hearts of the 94 patients with acute occlusion was only 50 per cent above normal. The concept of relative ischemia as a cause of heart failure in hypertrophied hearts which reveal very little or no atherosclerosis, is not accepted by Harrison and Wood (1949). They maintain that focal myocardial fibrosis (indistinguishable from healed infarcts but unassociated with coronary occlusion) should be attributed to a diminution of coronary flow "during a phase of cardiac failure" rather than to relatively small arteries or spasm. Karsner (1955) states that he has not seen myocardial infarction without organic occlusion of the coronaries, an opinion which differs from that generally held.

Infarction of Muscle Bundles. Monckeberg (1924) stated that scarring may be confined to the inner or outer layer or may involve the entire wall. He referred to Aschoff who believed that the site of necrosis of the ventricular wall was always the middle layer. The ventricular muscle bundles have specific functions and apparently each has its own blood



Figure VIII-26. Acute serofibrinous pericarditis associated with fresh myocardial infarction of two days' duration. X 150. (WCGH, 40 A 455.)



Figure VIII-27. Old healed subendocardial infarct. (WCGH, 50 A 220.)

supply (Robb and Robb, 1942). The function of the superficial muscles is to fix the apical fulcrum and the atrioventricular valve leaflets, the function of the deep muscles is chiefly expulsive. Lowe (1939) reconstructed myocardial scars in 5 hearts and decided that their position was consistent with one of the muscle groupings. He suggested that the scars represented a type of infarct which resulted from interference of blood supply to a portion of a muscle bundle. Price and Janes (1943) described the occurrence of a large sheet-like subendocardial infarct (Figure VIII-27) involving the dorsal wall of the left ventricle from the base of the atrioventricular ring to the apex; it also included the posterior papillary muscle and the ventricular septum throughout its length and extended onto the ventral wall of the ventricle in the middle and distal portions. They thought that the infarct corresponded to a muscle grouping in the ventricle, that of the subendocardial portion of the superficial bulbospiral muscle, rather than to the distribution of a main coronary vessel. Small myocardial scars (Figures VIII-28 and 29) are usually to be attributed to occlusion of small branches of the coronary arteries; but in hearts with evidence of old rheumatic dis-

ease, it is possible that some of the scarring has been produced by the rheumatic disease (Karsner, 1955).

Wartman and Souders (1950), in a study of 50 hearts having a total of 72 myocardial infarcts, determined that the pattern of every infarct corresponded to that of one or more of the four principal muscle bundles of the heart (Figures VIII-30 and 31). They classified their ventricular infarcts as full-thickness (entire thickness of ventricular wall), massive (but not full-thickness), and laminar or rim-like. The first two types commonly involved more than one muscle bundle; the last type usually involved only one bundle. Rupture occurred only in full-thickness infarcts, and aneurysm and mural thrombosis were more likely to occur in such infarcts. They encountered infarcts involving more than one bundle much more often than infarcts of a single bundle; the prognosis is worse in the former condition than in the latter. According to Edwards (1957), *transmural infarcts* are produced by complete arterial occlusion, while subendocardial infarcts are caused by chronic narrowing of the lumen. As may be expected, transmural infarcts are encountered twice as often as subendocardial infarcts among patients who die of acute infarction.

Cause of Death in Myocardial Infarction.



Figure VIII-28. Small myocardial scar of infarct resulting from closure of small branch of anterior descending coronary artery. (WCGH, 49 A 44.)

The commonest cause of death in myocardial infarction is a thrombotic or embolic lesion. Such lesions account for approximately one-third of deaths. Other common causes are *progressive circulatory failure, shock, and cardiac rupture*. In cases of sudden death in which no other lesion is demonstrable, death is presumed to have been caused by a disturbance in the conducting mechanism, such as heart block or ventricular fibrillation. In most instances, the occurrence of cerebral infarction in patients who have had a recent myocardial infarct, is not the result of an embolus from a mural thrombus but rather the result of a thrombus that develops in an atherosclerotic cerebral artery. The presence of a myocardial infarct appears to favor coagulation of blood and secondary thrombosis in other organs (Hellerstein and Martin, 1947).

Sequelae of Myocardial Infarction

Sudden death during or following an attack is caused in most instances by *shock* or by *arrhythmia*, presumably ventricular fibrillation

(Selzer, 1948). Those who survive the immediate attack may develop *left ventricular failure* or may die later from arrhythmia or from *embolism* to the arteries of the brain, lung, mesentery or extremities, or from recurrent myocardial infarction. Occasionally right ventricular failure supervenes and this may be further complicated by the occurrence of *pulmonary embolism* (from systemic veins or right side of heart) or pneumonia. Blumgart and co-workers (1940) concluded that death results whenever a sufficiently large area of myocardium undergoes ischemia, with or without necrosis, or when ischemia causes asystole, ventricular fibrillation or congestive failure.

Pericarditis. The incidence at autopsy of pericarditis following infarction varies considerably in different series of cases, as may be seen by the following figures: Yater and associates (1948c), 15.5 per cent; Wartman and Hellerstein (1948), 28 per cent; Bean (1938), 32 per cent; Feil, Cushing and Hardesty (1938), 62 per cent, and Stewart and Turner (1938), 80 per cent. In



Figure VIII-29. Microscopic infarct in heart that also had many thickened arterioles and "sulfonamide myocarditis." X 140. (A 26AQ, University of Michigan; WCGH, 58 P 479.)

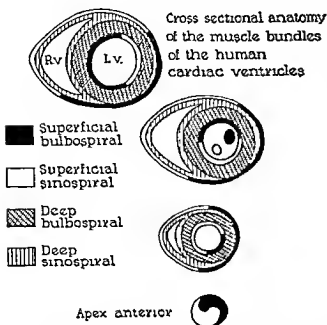


Figure VIII-30. Localization of myocardial infarcts with respect to muscle bundles of the heart. (From Wartman, W. B., and Souders, J. C.: Localization of myocardial infarcts, *Arch. Path.*, 50:329-346, 1950. Courtesy of the authors and *Archives of Pathology*.)

Bean's series, an effusion of 50 ml. or more was present in 15 per cent; hydrothorax was frequent and usually was greater on the right side. In the series reported by Stewart and Turner, pericarditis when present was localized in 75 per cent of cases and generalized in the others. The pericarditis is, of course, the result of extension of the infarction to the epicardial surface.

Mural Thrombosis. Until recent years, mural thrombi were encountered at the site of infarction in approximately 50 per cent of infarcted hearts (Blumer, 1937; Bean, 1938). Since the introduction of anticoagulant therapy (Dicumarol or heparin) in the treatment of patients with acute myocardial infarction, the incidence of mural thrombosis as well as of secondary embolism which follows mural thrombosis has been significantly reduced (Wright *et al.*, 1948; Schilling, 1950). Although mural thrombi usually form as a result of extension of the infarct to the endocardium, they may also form as a result of localized dilatation of the infarcted wall (Figure VIII-32). Bean found some thrombi still remaining 3 years after the acute infarction. As would be expected, mural thrombi are found most frequently, in association with myocardial infarction in the left ventricle.

They occur less often in the atria and least often in the right ventricle. In 46 cases of recent myocardial infarction studied by Levine and Brown (1929), there was gross evidence of mural thrombosis in 38 and of pericarditis in 24; only 3 hearts showed no gross evidence of either mural thrombosis or pericarditis.

Embolism or Systemic Thrombosis Following Mural Thrombosis. The commonest sites of embolism in order of frequency are lungs, kidneys, spleen, brain, lower extremities (femoral arteries) and intestines (mesenteric arteries). Systemic embolism occurs in approximately one-third of patients having mural thrombi in the left ventricle and appears to be particularly frequent when the thrombus is attached to the ventricular septum (Bean, 1938). The lungs are the commonest site of embolism in patients with myocardial infarcts, but usually pulmonary embolism is less serious prognostically than embolism to the brain or to a large vessel of an extremity (Blumer, 1937). Pulmonary emboli take their origin



Figure VIII-31. Transection of the heart near the base, showing white laminar scar of an old posterior basal and lateral infarct of the subendocardial portion of the superficial bulbospiral muscle. External to this scar are dark rim-like fresh infarcts of the deep bulbospiral muscles. These new infarcts are actually parts of a single infarct. (Courtesy of W. B. Wartman and J. C. Souders and *Archives of Pathology*.)

principally from veins of the pelvis or lower extremities, particularly in instances of massive pulmonary infarction; they may also arise from mural thrombi in the right side of the heart.

Cerebral infarction develops in patients with myocardial infarcts more often as a consequence of cardiac failure than as a result of embolism from a mural thrombus. Bean and Read (1942) reported 8 instances of acute myocardial infarction in persons having associated central nervous system manifestations (coma in 4 patients, hemiplegia in 2 patients). At autopsy severe cerebral atherosclerosis was present but no evidence of embolism, thrombosis or hemorrhage. They attributed the symptoms to congestive heart failure with fall in blood pressure, reduction in circulation and anoxia of brain. Recurring transitory hemiparesis is attributed by Bean and associates (1949) to restricted blood flow rather than to vascular spasm. Scheinker (1951) has emphasized that *acute damage to the brain* may result from sudden fall in arterial blood pressure in myocardial infarction. As a result of reduction in blood supply to the brain, ischemic changes may develop in the cortical gray matter, basal

ganglia or medulla; and the white substance may become swollen. The leptomeninges may reveal pronounced passive hyperemia and venous thrombosis while the brain substance may be the seat of hyperemia of the smaller veins and capillaries, perivascular edema or petechial hemorrhages. The resulting functional changes may be mild or serious, transitory or protracted, depending on the severity and duration of the basic physiologic disturbance in the heart.

Hadorn (1938) reported the occurrence of sudden death from embolism into the same coronary artery in which an earlier thrombus had resulted in myocardial infarction and secondary mural thrombosis. (See Figure VIII-44.) Ravdin and Wood (1941) reported successful removal of a saddle thrombus of the abdominal aorta in a physician, aged 32, 11 days after an attack of acute myocardial infarction. It must be borne in mind that the incidence of thrombosis and embolism, as given above, will be greatly decreased with the use of anticoagulants in the modern treatment of myocardial infarction.

Rupture of Heart. Rupture of the cardiac wall at the site of fresh or recent infarction occurs in approximately 8 per cent of cases.



Figure VIII-32. Old myocardial infarct with mural thrombus at site of aneurysmal dilatation of ventricle. Severe sclerosis and narrowing were present in the anterior descending branch of the left coronary artery. (WCGII, 45 A 172.)



Figure VIII-33 Fresh anterior apical infarct involving entire thickness of ventricular wall, with rupture. (WCGH, 36 A 105.)

Among mental patients, however, Jetter and White (1941) found a much higher incidence of rupture of hearts with acute infarction. In a series of 115 consecutive autopsies of mental patients who died suddenly or unexpectedly, 22 were found to have acute myocardial infarction. Sixteen of these (73 per cent) showed rupture of the cardiac wall at the site of the infarct. Most of these patients had chronic mental illness with intellectual deterioration. The commonest site of rupture is the lower third of the ventral wall of the left ventricle (Figure VIII-33) just above the apex (Monckeberg, 1924).

Krumbhaar and Crowell (1925) reviewed the literature of the preceding 50 years on spontaneous rupture of the heart. To 632 published cases, they added 22 others. They emphasized that cardiac rupture nearly always occurs in an acute myocardial infarct which is the result of occlusion of a coronary artery. Rupture occurred more often in men (58 per cent) and in persons 60 years or older (72.5 per cent). Most ruptures were of the left ventricle (80 per cent), probably because disease of the anterior descending branch of the left coronary artery was responsible for the infarct, and because of the relatively high pressure within the left ventricle; other sites included the right ventricle (10 per cent), the right atrium (6 per cent) and the left atrium (2

per cent). Of the left ventricular ruptures, 60 per cent involved the ventral wall, 23 per cent the dorsal wall and 15 per cent, the apex. Usually the tear was 1 to 2 cm. long, the edges irregular or jagged, and the external opening larger than the internal opening. In most instances, the rupture was associated with the presence of excessive epicardial fat, and generally the heart was enlarged.

Although Krumbhaar and Crowell found cardiac rupture more often in men, Zinn and Cosby (1950) encountered rupture twice as commonly in women (22) as in men (12), among 679 pathologically proved cases of myocardial infarction. Wessler and associates (1952) also found rupture relatively commoner in women, and attributed the greater frequency in women to the greater incidence of hypertension among women. In a series of 80 patients with cardiac perforation (Oblath *et al.*, 1952), 47 were women and 33 were men.

In a review by Edmondson and Hoxie (1942) of the protocols of 72 cases of cardiac rupture, rupture occurred in all portions of the heart except the dorsal wall of the right ventricle. This latter area is rarely the seat of infarction. Clowe and associates (1934) reviewed 34 cases of atrial rupture in the literature; of these, 48 per cent occurred before the age of 40 as compared to only 7 per cent of ventricular ruptures occurring before 40. In all but 2 of 40 ruptured hearts studied by Benson and associates (1933), the infarction was on the basis of sclerosis, thrombosis or embolism of the coronary arteries; 1 was probably of syphilitic origin and 1, a dissecting aneurysm involving the sinus of Valsalva, was caused by endocarditis from *Streptococcus viridans*.

Aarseth and Lange (1958) analyzed 89 instances of hemopericardium. In 8 instances the heart was not perforated; in 3 of these, the aorta was ruptured. All 81 cases of rupture of the heart were the result of acute myocardial infarction. These 81 represented 6.6 per cent of 1229 autopsies; 41 were men whose average age was 68.5 years, and 48 were women whose average age was 72.5 years. No instance of rupture was found in any man under 50 or woman under 60. Anticoagulants were given to 33 patients, 22 of whom died of cardiac rupture within 4 to 9 days. Of the 58 patients who did not receive antio-

agulants, 30 per cent died during the first day of illness, 51 per cent within the first 5 days, and 80 per cent within the first 10 days. The sites and frequency of rupture were: anterior wall, 43, posterior wall, 29, lateral wall, 1; apex, 8. In addition, 1 heart also had perforation of the ventricular septum. The precipitating cause of the rupture was not evident in most patients. In 1 patient, death occurred while walking to the bathroom, 1, following an enema, and 1 during infusion of saline solution. Rupture occurred in 8 of 72 patients (11.1 per cent) not treated with anticoagulants compared with 15 of 69 patients (21.7 per cent) treated with anticoagulants. The author cited 4 other series of cases which specified the number of patients treated or not treated with anticoagulants and the number of hearts found ruptured at autopsy. If all of these 5 series are combined, we obtain a total of 627 patients who did not receive anticoagulants, of whom 65 developed rupture, an incidence of 10.4 per cent. This compares with a total of 240 patients who were treated with anticoagulants, 57 of whom developed cardiac rupture, an incidence of 23.7 per cent. Therefore, during the first two (or three) weeks following acute myocardial infarction, the danger of cardiac rupture is appreciably increased if anticoagulants are used.

Time of rupture. Rupture of the heart may occur as early as 1 day and as late as 4 weeks after onset of infarction, but is commonest during the first week. The average time of occurrence is 7 days. If rupture occurs 3 or more weeks after infarction, it is likely that a complication is present, such as another acute infarct (Mallory *et al.*, 1939). Following perforation into the pericardial sac, death is usually sudden or occurs after a few minutes. In 90 per cent of 400 ruptured hearts, the time of survival was 12 hours or less after onset of rupture (Krumbhaar and Crowell, 1925).

In the case of ventricular septal perforation (Figures VIII-34 and 35), survival is often longer, varying usually from several hours to several days; sometimes the patient survives for several months or years. The patient of Wood and Livezey (1942) lived nearly 5 years following this complication. Rupture of the ventricular septum may be diagnosed during life (Fowler and Failey, 1948) on the basis of the history and findings of myocardial infarction and the development of signs of a ventricular septal defect, and particu-

larly the sudden appearance of a thrill and a loud harsh systolic murmur along the lower left sternal border; and of right ventricular failure. Rupture of the ventricular septum may be confused with rupture of a papillary muscle of the left ventricle following myocardial infarction. In rupture of the papillary muscle, the murmur is louder and nearer the apex and there is left ventricular failure. Carroll and Cummins (1947) reported, in a 60-year-old man with coronary occlusion and myocardial infarction, rupture of the ventricular septum followed by rupture of the posterior wall of the left ventricle.

Predisposing causes of cardiac rupture are absence of old myocardial scars and presence of heavy infiltration of leukocytes, hemorrhage and increase in subepicardial fat in the region of infarction, and undue exertion or persistence of hypertension after onset of infarction. Edmondson and Hoxie believe that old scar tissue in the region of fresh infarction may lessen the chance of perforation because of the presence in the scarred areas of increased collateral circulation, because of greater re-



Figure VIII-34. Perforation of interventricular septum in area of old and recent infarction. The walls of the defect were undergoing organization and a thrombus was attached to the inferior portion of the defect. (Courtesy of Dr. J. L. Chason, Veterans Administration Hospital, Dearborn, Michigan.)

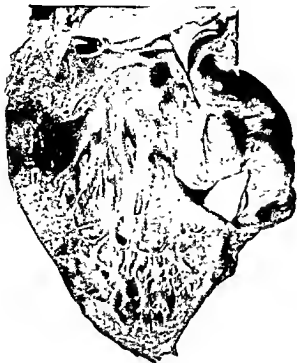


Figure VIII-35. Large defect in interventricular septum at inferior portion of old posterior basal aneurysm. The defect measured 2 cm. in diameter and its walls were smooth. The defect in the upper portion of the figure was made by the cutting knife. (Courtesy of Dr. J. L. Chason.)

sistance of the fibrous tissue to ischemia and because of the support the fibrous tissue gives to the necrotic muscle.

The accumulation of leukocytes in the infarcted myocardium may conceivably liberate *proteolytic enzymes* which may contribute to softening of the necrotic muscle and thus add to the danger of rupture. According to Lowe (1947), perforation is not likely to occur in a direct line but rather to follow the interfaces between the spiral muscles. Rupture occurs in full-thickness infarcts; these are common at the apex of the left ventricle which is composed entirely of superficial muscle bundles, and rare at the base of the heart which is chiefly composed of deep muscles (Wartman and Souders, 1950).

Howell and Turnbull (1950) found *old healed infarcts* in 4 of 8 hearts that ruptured following acute infarction. They did not, however, indicate the relation of the old infarcts to the sites of the fresh infarcts or rupture. An old healed septal defect following perforation of the infarcted septal muscle was reported by Gross and Schwartz

(1936) to be circular, "several" centimeters in diameter, and to have smooth regular edges.

Experimentally also, it has been shown that in fresh infarction from recent occlusion (without associated old infarction or coronary narrowing), the heart is particularly susceptible to rupture because of the absence of previously developed collateral anastomoses (Blumgart *et al.*, 1955). Oblath and associates (1952) found that most ruptures occurred after dissection of the infarcted myocardium, and only a few were "blow-outs."

In a careful study of 20 ruptured hearts, Wessler and associates (1952) found that rupture usually occurred between the fourth and eleventh day after onset of acute myocardial infarction, that the patient usually had *hypertension* but no previous history of old myocardial infarction or congestive failure, and that persisting hypertension or excessive effort usually preceded rupture. The infarct was generally transmural, the affected region of the myocardium being poorly supplied by collateral circulation and having no fibrosis.

Physical exertion during the act of defecation may induce rupture. Howell and Turnbull (1950) reported that, of 8 patients with cardiac rupture following acute infarction, 2 collapsed in the bathroom of their home, a third while using a bedside commode, and a fourth patient died while using a bedpan.

McNamara and associates (1937) reported cardiac rupture from weakening of the myocardium by metastatic carcinoma. Gladden (1943) collected from the literature 9 cases of myocardial abscess with cardiac rupture and added 1 case. None of the 10 patients had any cardiac symptoms prior to the rupture.

Hemopericardium. The commonest cause of hemopericardium is rupture of the myocardium. Other common causes include trauma, and perforation into the pericardial sac of a dissecting aneurysm of the first portion of the ascending aorta. Hemopericardium is also found in some instances of metastatic neoplasm involving the pericardium. In fatal hemopericardium from tamponade following rupture of the myocardium, the amount of blood in the pericardial cavity has been estimated to vary from 150 to 700 ml., and in the majority of cases from 200 to 250 ml. (Edmondson and Illovic, 1942). Munck (1916) found an average volume of 350 ml. of sanguineous fluid in the pericardial sac in 10 cardiac perforations among men, and an average

of 270 ml. of fluid in 10 women. The slower the escape of blood into the pericardial cavity, the larger the amount that can be tolerated. In chronic disorders, like tuberculous pericarditis, as much as a liter or more of fluid (not necessarily bloody) may accumulate gradually, the heart having had time to adjust itself to the great distension of the pericardial sac.

Anderson and co-workers (1952) reported 3 cases of hemopericardium complicating myocardial infarction in the absence of cardiac rupture. Two of the patients came to autopsy; 1 had had anticoagulant therapy. In all 3, the hemorrhage was attributed to bleeding from the pericardial granulation tissue. The authors pointed out that, in such cases, aspiration of the fluid from the pericardium cavity may be life-saving.

Ventricular Failure Following Myocardial Infarction. Cardiac failure occurring in myocardial infarction is usually attributable to failure of the left ventricle. Most patients with left heart failure also develop insufficiency of the right ventricle, the manifestations of which then dominate the clinical picture (Fishberg, 1932). This may occur especially in patients who, in addition to the left heart failure, have chronic pulmonary disease and right ventricular hypertrophy. Failure of the right ventricle is particularly likely to ensue following perforation of the infarcted ventricular septum. In this case the right ventricle must withstand the higher pressure transmitted from the left ventricle with which it communicates.

Bernheim's syndrome. Encroachment of the ventricular septum upon the cavity of the right ventricle, as in hearts with severe left ventricular hypertrophy or in infarction of the septum, has sometimes been held responsible for the so-called Bernheim's syndrome, in which the patient develops symptoms of right heart failure with distention of the veins of the neck and injection of the facial veins, followed by cyanosis, edema of the lower extremities and congestion of the liver, but without accompanying pulmonary edema. Peel (1948) reported a dissecting aneurysm of the ventricular septum secondary to calcification of the coronary arteries and thrombotic occlusion of the anterior descending branch of the left coronary. The aneurysm formed a swelling 38 by 28 mm. and projected into the cavity of the

right ventricle (Bernheim's syndrome) for an extent of 15 mm. The progressive right ventricular failure in this patient was attributed, in part, to obstruction of the outflow tract of the right ventricle by protrusion into it of the septal aneurysm and, in part, to disease of the myocardium. Evans and White (1948), in a study of the clinical and pathologic findings in 33 patients in whom the heart weighed more than 750 grams, did not encounter a single unquestionable example of "Bernheim's syndrome" and recommended that the designation be dropped. Fishberg (1940) and others (Atlas *et al.*, 1950, Russek and Zohman, 1950), however, support the validity of this syndrome. The development of cardiac hypertrophy as a result of cardiac failure that follows myocardial infarction has been previously mentioned (page 546).

Spontaneous Rupture of Papillary Muscles. Davison (1948) reviewed the clinical and pathologic findings in 31 reported cases of spontaneous rupture of papillary muscles. Rupture of the papillary muscles of the right ventricle was encountered only twice, both as a result of involvement by bacterial vegetations. Among instances of rupture of the papillary muscles of the left ventricle, the posterior muscle (Figure VIII-36) was affected twice as often as the anterior. In 2 instances perforation appeared to have been caused by syphilis; all others were associated with coronary atherosclerosis and most of these, with coronary occlusion and myocardial infarction. Davison's 3 cases were encountered among 14,000 autopsies, and in 1 of these, the diagnosis had been made antemortem. He ascribed the greater frequency of involvement of the posterior muscle to its remoteness from the source of blood supply, and perhaps to a poor collateral blood supply to the superficial bulbospiral muscle which forms the left posterior papillary muscle. On the other hand, the left anterior papillary muscle is a favorite site of scarring (Mönckeberg, 1924, p. 397). The left anterior papillary muscle derives its blood supply only from the left coronary artery (from a branch of the left anterior descending ramus) and lies at the greatest distance from the ostium of the artery (Gross, 1921); the left posterior muscle receives branches from both coronaries.



Figure VIII-36. Rupture of posterior papillary muscle of left ventricle. Heart weight 1025 Gm. A "rising" systolic apical murmur was transmitted to the anterior axillary line. The patient, aged 40, was in severe congestive failure during the last 6 weeks of life. (WCGH, 34 A 64.)

Smith (1950) reported 2 instances of spontaneous rupture of the left posterior papillary muscle in its midportion, associated in each instance with recent thrombosis of the right coronary artery. Each patient died in circulatory collapse 3 days after the onset of the attack. Smith stated that in 18 of 33 reported cases, the rupture was the result of thrombosis of a coronary artery and was associated with infarction of the myocardium, the posterior papillary muscle of the left ventricle was ruptured in 13 patients, in 11 of whom there was thrombosis of the right coronary artery or of the circumflex branch of the left coronary. Rupture of the anterior papillary muscle of the left ventricle followed coronary thrombosis in 5 persons, in 3 of whom the left circumflex or anterior descending branch was involved and in 2, the right coronary.

Most patients die suddenly and almost immediately after rupture of a papillary muscle. In 1 patient, life persisted 10 months following rupture; in another, 20 months. One patient stated that he believed a muscle had broken over the heart. (See Stevenson and Turner, 1935.) The diagnosis should be considered if a patient with evidence of myocardial infarction develops a change in the character and intensity of a mur-

mur which was present prior to the infarction. The new murmur is usually located over the mitral area, is systolic in time, and loud and harsh in character. The condition must be distinguished from rupture of mitral chordae tendineae, rupture of an aortic cusp, and acute perforation of an infarcted interventricular septum or ventricular wall. Traumatic rupture of the papillary muscles has also been reported (Glendy and White, 1936, Payne and Hardy, 1937), and Smith (1950) mentions an unreported case in which rupture was attributed to *polyarteritis nodosa*.

Abscess Formation in Myocardial Infarct. Miller and Edwards (1951) reported the occurrence of an abscess in an acute myocardial infarct. The infecting organism, *Escherichia coli*, was believed to have been derived from the right kidney which was the seat of acute pyelonephritis. The authors encountered reports of 3 other cases of abscess associated with acute myocardial infarct; in each of these the abscess was believed to have been a complication of a pyogenic pneumonia, and in one of these (Case I, Tedeschi *et al.*, 1950), the heart had ruptured.



Figure VIII-37. Large left ventricular aneurysm. (WCGH, 47 A 301.)



Figure VIII-38. Section of left ventricular aneurysm (same as Figure VIII-37) showing large laminated mural thrombus.



Figure VIII-39 Old posterior basal infarct with aneurysm of wall. Also note fresh occlusion with hematoma in left circumflex artery with fresh patchy hemorrhagic infarction of lateral wall of left ventricle. (WCGH, 37 A 337.)

Rupture of Coronary Sinus. Hinshaw and Brown (1949) reported rupture of the coronary sinus as a result of involvement of the sinus in an area of recent myocardial infarction at the base of the lateral wall of the left ventricle, following atherosclerotic occlusion of the left circumflex artery near its origin.

Trophic Changes in Hands Following Myocardial Infarction. In 18 patients with clinical thrombosis and in 4 others with persistent angina pectoris, Askey (1941) observed a syndrome of pain and restriction of movements of one or both shoulders and of stiffness, pain and swelling of one or both hands. Seven of the patients had Dupuytren's contracture. The syndrome was explained by a reflex induced by myocardial ischemia, afferent fibers for painful stimuli from the heart connecting with afferent fibers for pain from the shoulder. Kehl (1943) reported 6 cases of Dupuytren's contracture (bilateral in 5) as a sequel to coronary occlusion. He felt that irritation of the sympathetic ganglia, consequent upon the coronary disease, was a possible factor. John-

son (1943) observed disabling changes in the hands, resembling sclerodactylia, in 39 of 178 consecutive cases (21 per cent) of acute myocardial infarction, and suggested that they were caused by ischemia of the tissues of the fingers resulting from reflex vasoconstriction of the arteries of the hand induced by cardiac pain.

Aneurysm of Ventricle. A cardiac aneurysm represents bulging of a diseased weakened cardiac wall in response to the intraluminal pressure. About 85 per cent of such aneurysms are caused by coronary occlusion (Sternberg, 1914). Cardiac aneurysms most often involve the left ventricle, those of the right ventricle being rare, and those of the atria exceedingly rare (Monckeberg, 1924). Anterior apical aneurysms (Figures VIII-37 and VIII-38) show bulging of an infarcted area that is generally 3 to 5 cm. or more in diameter, while posterobasal aneurysms (Figure VIII-39) produce a lesser degree of bulging in an infarcted area and generally measure 2 to 3 cm. in diameter. In the case reported

by Shennan and Niven (1925), the greatest diameter of the aneurysm was 16 cm.

Among 160 myocardial infarctions, Wartman and Hellerstein (1948) found 35 (22 per cent) with ventricular aneurysm, all in the left ventricle. Of this number, 25 were in the anterior apical portion, 3 in the posterolateral portion and 7 in the posterobasal region. Most of the aneurysms had mural thrombi. Among 114 hearts with gross infarcts, Yater and associates (1948c) encountered 4 with ventricular aneurysms (3.5 per cent). Two of these aneurysms were the result of fresh infarcts and 2 the result of old infarcts. Betsch (1945) found 11 cardiac aneurysms among 141 cases of myocardial infarction (8 per cent), while Parkinson and associates (1938) determined from published postmortem statistics of 6 separate groups of observers that cardiac aneurysm occurred in 9 per cent of cases of infarction. Among 7200 autopsies, Betsch found an incidence of 1.5 per 1000 autopsies. Lucké and Rea (1921) found an incidence of 1.1 per 1000 in a series of 12,000 autopsies. Fujinami (quoted by Monckeberg, 1924) reported occurrence of 3 ventricular aneurysms in a 75-year-old woman with severe atherosclerosis.

Ventricular aneurysms of atherosclerotic etiology appear to develop particularly during the period of myocardial necrosis and softening, especially during the first 2 weeks after coronary occlusion (Fulton, 1941). Ball (1938) expressed the belief that the development of a ventricular aneurysm is favored by permitting the patient to be up and around too soon, *i.e.*, within a week or two after the development of acute infarction. Evidence to support this belief is found in the work of Sutton and Davis (1931). These investigators exercised dogs following coronary ligation, and sacrificed the animals after an interval sufficiently long to permit healing of the myocardial infarct. One animal was given a rest of 6 days after ligation; the infarcted area was well scarred without thinning of the ventricular wall. In 4 other animals, exercise was started within 3 days of the operation; their hearts presented thin scars with aneurysmal bulging.

Penner and Peters (1946) reported survival of 15 years following onset of occlusion; they be-

lieved that the aneurysm of the left ventricle was present for 15 years. The long survival was attributed to an extended period (1 year) of hospitalization after onset of symptoms of infarction. Joachim and Mays (1927) encountered a large left ventricular aneurysm at autopsy in a man of 25 who died suddenly; the anterior descending branch of the left coronary artery was occluded near its origin. The patient had suffered multiple fractures of the ribs of the left side when he was run over by a wagon at the age of 12.

Causes of ventricular aneurysm, other than atherosclerosis. Parkinson and associates reported ventricular aneurysm following necrosis of the myocardium caused by rheumatic fever. Cardiac aneurysms may also be caused by gumma, infective endocarditis with abscess of the myocardium, particularly in association with mycotic coronary arteritis, congenital defects and trauma.

Grossly the aneurysm may be saccular but more often it is not sharply demarcated from the ventricular cavity. The endocardial surface is frequently the seat of a mural thrombus. The wall of the aneurysm, exclusive of any mural thrombus which may be attached, is thinner (Figure VIII-40) than that of the ventricle prior to infarction. Its thickness is



Figure VIII-40. Old infarct and aneurysm involving lower two-thirds of right ventral wall of left ventricle and lower and ventral three-fourths of septum. The patient was a man of 68 who died from the effects of carcinoma of the prostate rather than from heart disease. (WCGH, 33 A 361.)



Figure VIII-41A. Pseudoaneurysm of left ventricle, formed as result of perforation of infarcted posterolateral wall of ventricle into pericardial sac. Aneurysm is seen from aspect of opened pericardial pseudodiverticulum. Courtesy of Dr. Clyde O. Hurst, Henry Ford Hospital, Detroit. (WCGH, 58 P 482.)

determined by the amount of muscle destroyed, the extent of scarring and contraction of scar tissue and the degree of bulging caused by the intraventricular pressure. Monckeberg (1924) pointed out that adhesions between the epicardium and pericardium in the region of the aneurysm may serve as a protective measure against an otherwise fatal hemorrhage into the pericardial cavity.

Microscopically the muscle fibers are decreased in size and often in number, and there are various degrees of necrosis, fibrosis, hyalinization and, sometimes, deposits of calcium in the infarcted area. The degree of myocardial softening seems to be a predisposing factor in spontaneous cardiac rupture following myocardial infarction (Edmondson and Hoxie, 1942).

The larger ventricular aneurysms may be diagnosed clinically on the basis of a history of coronary occlusion, electrocardiographic changes, enlargement of the heart, particularly to the left, and radiologic examination indicating changes in the character of the apical pulsation and alteration in size, shape and contour of the heart. In anterior aneurysms, a "ledge" or bulge (Figure

VIII-37) in the cardiac border may be seen on x-ray examination when the patient is placed in the right oblique position, while posterior aneurysms (Figure VIII-39) may sometimes be seen with the patient in the left oblique position. Aneurysm or perforation of the interventricular septum may cause enlargement of the heart to the right. Sometimes calcification occurs in the wall of an aneurysm and may be seen in roentgenograms. On fluoroscopic examination, an aneurysm located between the apex and the base may produce a localized area of pulsation in this area.

Riederer and Themel (1955) reported occurrence of a pericardial *pseudodiverticulum* subsequent to rupture of a myocardial infarct in a 67-year-old man who survived the acute infarction for 5 months. We have observed a similar case of Dr. Clyde O. Hurst of Henry Ford Hospital, Detroit, in which the patient died 6 years after the clinical detection of a left ventricular *pseudoaneurysm* (Figure VIII-41A and B). In both of these cases, the wall of the pseudoaneurysm was formed by pericardium, and a pre-existing pericarditis was thought to have produced a localized hemopericardium and the subsequent development of a fibrous thick-walled pseudoaneurysm which communicated with the chamber of the left ventricle through relatively small openings.

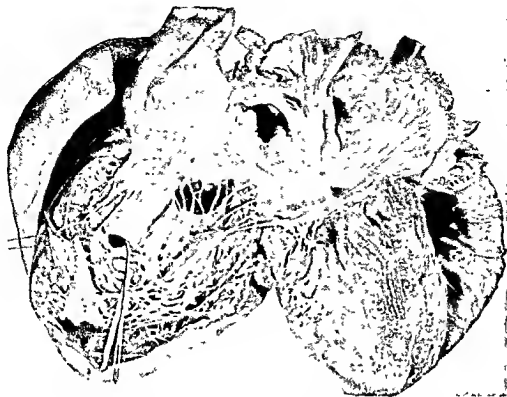


Figure VIII-41B. Pseudoaneurysm of left ventricle shown in Figure VIII-41A, seen from interior of left ventricle. Posterolateral wall is perforated in region of muscular attachment of chordae tendineae of posterior leaflet of mitral valve.

Calcification of Myocardium may be the result of inflammatory, degenerative or vascular lesions. Plaque-like areas of calcification (Figure VIII-42) may be found (principally by radiologic examination) in old myocardial infarcts and particularly in the wall of an aneurysm (Brean *et al.*, 1950). Calcification must be distinguished from that occurring in the pericardium as a result of an old tuberculous or purulent inflammation. Finestone and Geschickter (1949) briefly reviewed the literature on myocardial calcification and found that the commonest lesion in which calcification occurred was an old myocardial infarct. In addition to their own case, they mentioned 5 others in which bone formation was associated with the calcification.

Spontaneous Rupture of Cardiac Aneurysm. Spontaneous rupture of a cardiac aneurysm is rare, the usual terminal event being cardiac failure; rupture of the heart wall following coronary occlusion is more likely to occur during the first 10 days after onset of the infarction.

Betsch (1945) reported 2 instances of spontaneous rupture among 11 patients with cardiac aneurysm. Betsch's first case was a 40-year-old man whose first attack of infarction occurred 4 months before death. He had a ventricular aneurysm, 10 cm. in diameter, which still showed an organized mural clot. In his second case, the aneurysm occurred in a 52-year-old man with no previous cardiac history and appeared to be of recent origin. Fisher's (1945) patient was 67 years of age and died of rupture of a cardiac aneurysm 11 weeks after onset of symptoms of infarction. This patient appeared to have had adequate rest following the myocardial infarction. Almost always rupture of the heart occurs in a fresh myocardial infarct but Brown and Evans (1940) reported an instance of cardiac rupture through a calcified myocardial infarct after the formation of a myocardial aneurysm. They suggested that this occurred as a result of the localization in the aneurysm of an inflammatory process secondary to bacteremia from a perinephric abscess. In an instance of rupture of a ventricular aneurysm encountered by Yater and associates (1948c), the aneurysm appeared to be the result of a fresh infarct. Rupture of a ventricular aneurysm may also be traumatic (Monekeberg, 1921).

Betsch (1945) reported 2 instances of spon-

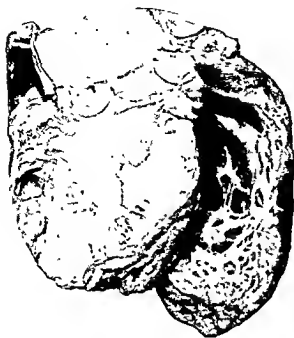


Figure VIII-42 Multiple old healed infarcts. The wall of the aneurysm was the seat of calcification (WCGH, 34 A 29.)

Atherosclerotic Aneurysm of Coronary Artery. A small proportion of aneurysms of the coronary arteries develop on the basis of atherosclerosis. In a review of the literature, Mitchell (1947) encountered 17 instances of atherosclerotic aneurysm. In 5 of these, rupture and death ensued, in the others, the finding was incidental. For a discussion of aneurysm of coronary arteries from other causes, see pages 637 and 639.

Prognosis

Survival after Onset of Angina Pectoris, Coronary Occlusion or Myocardial Infarction. Survival depends on a number of factors, including the nature and extent of the arterial disease, previous occurrence of infarcts, the severity of the attack, the presence of shock, the amount of muscle damage, and the development of arrhythmias, congestive failure or complications, particularly thrombosis and embolism.

Coombs (1932) pointed out that the prognosis depends more on the *severity of the attack* than upon the state of the patient before the attack. He believed the degree of reduction in pulse

pressure to be the single most important sign; that a considerable fall in systolic pressure was significant, and that extreme pallor was an ominous sign. With the increasing recognition of milder forms of coronary occlusion and with improved methods of treatment, the mortality rate is diminishing. The vast majority of patients recover from the initial attack of occlusion. The prognosis becomes more serious with *succeeding attacks*.

In their study of heart failure from coronary "thrombosis," Master, Dack and Jaffe (1937) found that the *mortality rate* was 4 per cent in the absence of failure and 30 per cent in the presence of failure. In failure of the left ventricle alone, the mortality rate was 4 per cent; in failure of both ventricles, the rate was 40 per cent. The *average age* of those who died without evidence of cardiac failure was 49 years; of those with heart failure, 57 years. They found the following *signs associated with heart failure* and with a *poor prognosis* in acute coronary occlusion: pulse rate of 100 or more, pulse pressure of 20 mm. or less, muffled or "tic-tac" heart sounds, diastolic gallop rhythm, respiratory rate over 26 per minute, cyanosis, orthopnea, edema of lungs, fever above 101° F. and severe shock. Arrhythmias were usually transient and did not alter the prognosis but, according to Thompson and Levine (1936), the prognosis is made worse by the occurrence of pulsus alternans, especially if it appears within a number of hours or a few days after the onset of acute infarction. Master and associates believe that hypertension, although an etiologic factor in coronary occlusion, apparently has little effect on the mortality rate. The mortality rate rose from 11 per cent in the first attack to 50 per cent in the third attack.

Drake (1940) thought that the *immediate mortality* of coronary "thrombosis" under the best conditions is about 15 per cent. Drake quoted references to reported cases with survival of 18 years and 24 years and reported survival of a patient for nearly 40 years after an initial attack of myocardial infarction at the age of 40. Master and associates (1943) found that when the *systolic blood pressure* fell below 80, the patient usually died; the height of the blood pressure did not significantly influence the future course of the patient with respect to subsequent angina pectoris, heart failure, coronary occlusion or death.

White and co-workers (1943) studied the duration of disease in 497 patients with *angina pectoris*. Of the 445 patients who had died up

to the time of their report, the average duration of the disease was 7.9 years. The average duration in the 52 persons who were still living was 18.4 years, and it was estimated that the average duration for the entire group would be about 10 years. Parker and associates (1946) made a follow-up study of 3440 patients with angina pectoris. The mortality rate for this entire group during the first year after diagnosis was 18 per cent, and approximately 10 per cent annually among survivors in each subsequent year. The rate was higher for men than for women, and for patients in the fourth decade than for those belonging to older decades. The rate was higher also in the presence of cardiac hypertrophy, hypertension, congestive heart failure, significant electrocardiographic abnormalities, and previous myocardial infarction. Smith and associates (1951) found that the mortality rate was not increased among their patients who had a history of antecedent angina. In the series of Zoll and associates (1951e), however, a more serious prognostic impact was evident. Of 177 patients with angina pectoris, one-third were dead within 1 year after the onset of angina, half were dead within 2 years, three-fourths were dead within 5 years, and nine-tenths within 10 years. While these figures would seem to indicate that the prognosis among patients with angina is better than among those with myocardial infarction, in general, patients who have had angina who are hospitalized and come to autopsy are likely to have been more seriously ill than those who die of angina at home.

Chambers (1946) observed 100 consecutive patients (average age, 59 years) in their initial attack of acute myocardial infarction. Thirty-four died within 1 month and another 8 within a year. Of the 58 who survived 1 year, 9 had nonfatal recurrent infarctions. The average age of those who died was 3 years greater than that of the survivors. He found (1947) antecedent hypertension in 74 per cent of patients, but no relation between antecedent hypertension and the mortality rate. An early return of the blood pressure to normal or to hypertensive levels existing before occlusion was a good prognostic sign; in the fatal group the blood pressure did not return to its former level.

Master (1947) estimated the mortality rate from all cases of acute coronary occlusion to be less than 20 per cent, and for the first attack, to be less than 10 per cent. Katz (1947) determined that about one-fifth of patients studied with recent myocardial infarction died during their hos-

pital stay, and that the average expectancy of life following an infarct was 5 years. He found that some patients lived comfortably for over 20 years following an infarction. Patients whose blood pressure fell markedly and patients in shock had a poor prognosis. He stated that infarction is more benign than is generally appreciated, that it usually is self-limited; and that by the time the clinician sees the patient, the latter is already convalescing.

Yater and associates (1948c) determined that shock occurred in 17 per cent of their patients with coronary artery disease at the onset of the attack, and that it was 8 times as common in men who died as in those who survived. As a rule, younger patients lived longer; also, as a rule, the greater observance of caution by the patient following recovery from the effects of coronary occlusion, the longer will he live (White and Bland, 1931).

Katz and associates (1949) also studied the length of survival of 507 patients hospitalized for recent myocardial infarction. They found that approximately one-fourth were dead at the end of 2 months, one-half at the end of 1 year, two-thirds at the end of the third year, and four-fifths at the end of 5 years. The group which had had heart failure or diabetes at the time of admission showed a greater mortality rate at the end of 2 months and for the entire period studied.

A rectal temperature above 104° F., a leukocyte count over 25,000 or a venous pressure over 200 mm. of water indicates a grave prognosis, according to Shillito and associates (1942). Seven of 8 of their patients showing any of these signs died within 16 days after the coronary attack. Although almost all of their patients showed an increase in the sedimentation rate, the degree of its increase was not found to be a reliable index to prognosis. Goodrich and Smith (1936) believed that a count of nonfilamented polymorphonuclear leukocytes in excess of 30 per cent after the fourth day of an attack of coronary occlusion constituted an unfavorable sign. Smith and associates (1951) noted that a high leukocyte count indicated a poorer prognosis. They calculated that the mortality rate in their series of patients with acute infarcts was 42 per cent among those who developed thromboembolic complications, as compared with 20 per cent among those who had no such complications. The therapeutic use of anticoagulants within recent years has significantly reduced the incidence of thrombosis and embolism following myocardial infarction and the mortality rate in this group of patients (Allen *et al.*,

1947; Wright *et al.*, 1948; Nichol and Borg, 1950; Smith *et al.*, 1951).

The prognosis for a diabetic patient with myocardial infarction is poor. Bradley and Bryfogle (1956) found that 57.7 per cent of patients who died from the first attack of infarction were diabetic.

Russek and Zohman (1954) studied the survival rates among 1318 patients who had acute myocardial infarction which was confirmed by electrocardiographic signs. Of 611 who were regarded as good risks on the day of admission, 3.4 per cent died and 1.3 per cent had thrombotic or thromboembolic complications, of 707 who were thought to be poor risks, 60 per cent died and 11.5 per cent had thrombotic or thromboembolic complications. The mortality rate for patients under 60 years was 30 per cent, for patients over 66 years, 40 per cent. The presence of any of the following conditions caused the patient to be classified as a poor risk: previous myocardial infarction, intractable pain, extreme or persisting shock, significant enlargement of heart, gallop rhythm, congestive heart failure, cardiac arrhythmias, diabetic acidosis, obesity, or previous history of thromboembolic phenomenon. Richards and associates (1956) made a follow-up study

for a period of 25 years of 200 patients with myocardial infarction who had been seen in consultative practice. Of the 200 patients, 38 died during the first 4 weeks; 79 survived 5 years; 50, 10 years; 23, 15 years; 8, 20 years; 6, 25 years, and one was alive 28 and another 29 years later. They regarded the degree of recovery following the acute period of infarction as the best index to long-term survival.

Weiss (1956) made a 10-year follow-up of 211 patients who recovered from a first infarct and lived more than 2 months. Of these, 77 (36.5 per cent) lived more than 10 years; the majority of them were in the younger age groups. Among those who died, the cause of death was cardiovascular disease in 88 per cent and cerebrovascular disease in 7 per cent. Weiss and Weiss (1958) conducted a 5-year follow-up study of 431 men in private practice who returned to work after suffering an attack of myocardial infarction. The average time of returning to work was 3 months. One third (143) of the patients worked less than 5 years. Of these, two thirds died and one third retired. The remaining two thirds of the patients (288) were at work after 5 years.

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Diseases of the Coronary Arteries

B. Non-atheromatous Lesions

S. E. GOULD

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Occlusive Lesions

Coronary Embolism. Most instances of coronary embolism are secondary to bacterial endocarditis (Figure VIII-43) of the left side of the heart. The anterior descending branch of the left coronary is the artery most commonly involved. Embolic occlusions of large coronary branches are usually single; emboli to small coronary branches are nearly always



Figure VIII-43. Septic embolus in branch of left anterior descending coronary artery, secondary to acute bacterial endocarditis caused by *Staphylococcus albus*. (WCGH, 40 P 317.)

multiple. In making a diagnosis of embolism at autopsy, one should be able to determine the source of the embolus. Absence of inflammation or of other lesion of the wall of the obstructed vessel at the site of the occluding material speaks in favor of the embolic nature of the occluding process. Hamman (1941) reviewed 30 cases in the literature of embolic occlusion of large branches and added 10 cases of his own. He estimated that from 1 to 2 per cent of cases of coronary occlusion are caused by embolism. He listed six possible sources of emboli of coronaries: (1) a thrombus or atheromatous material in a coronary artery; (2) a thrombus covering an atherosclerotic plaque at the root of the aorta; (3) a bacterial vegetation on the mitral or aortic valve; (4) an intracardiac mural thrombus; (5) a thrombus in a pulmonary vein; and (6) a thrombus in a peripheral vein (paradoxical embolism). Among the 40 collected cases, the source of embolism in 19 was a bacterial vegetation. The two organs that suffer most from the effects of infarction are the brain and the heart; cerebral embolism is more common than coronary embolism.

Saphir's (1933, Case 2) patient was a 70-year-old man with coronary sclerosis, thrombosis and myocardial infarction. The thrombus, present in the proximal portion of the circumflex branch of

the right coronary artery, partially occluded the vessel. It was estimated to be 6 days old. A portion of the thrombus then broke off and lodged distally at the site of origin of the posterior descending branch. The embolism caused sudden death. This finding illustrates the value of careful and complete dissection of the coronary arteries. Two similar cases, involving men aged 47 and 49, were reported by Jaffé (1940). A similar instance of embolism, in which the patient died as a result of ventricular rupture, is illustrated in Figure VIII-44. Hadorn (1938) reported the occurrence of thrombotic occlusion of a coronary artery with resulting myocardial infarction and mural thrombosis; a portion of the mural thrombus then broke off and lodged in the same coronary artery, causing sudden death of the patient. In pneumonia, embolism is rare since thrombi do not ordinarily form in the pulmonary veins. The veins may become thrombosed as a result of suppurative or invasion by tumor. Medlar (1935) reported plugging of a branch of the left coronary artery by a bit of caseous material containing tubercle bacilli. There was no evidence of previous disease of the artery. The patient had bilateral pulmonary tuberculosis, a small cavity in the upper lobe of the right lung and generalized miliary tuberculosis. In addition the lateral and upper portion of the left ventricle was the seat of an infarct, a few days old, which measured 3 by 1.5 cm. The patient died unexpectedly as the result of the embolism. Moragues and associates (1950) reported the occurrence of embolism with survival for several months. The source of the embolus was a nodular calcified mass on the aortic valve which had no associated bacterial endocarditis.

Shrader and associates (1956) reviewed the literature on coronary embolism. They encountered reports of 4 instances in which the diagnosis had been made during life. Of 81 cases encountered at autopsy, 54 were sufficiently documented to permit analysis. In 49 cases the age was stated, the average age being 39 years. Of 47 in which the sex was given, 35 were males and 12 were female patients. Of 47 instances in which the vessel involved was mentioned, in 36 the left artery and its branches were occluded; in 7, the right artery; and in 4, both vessels. In 54 cases the nature of the embolus was determined. The embolus arose from an endocarditis 22 times (in 17 the endocarditis was acute or subacute and affected one or both valves of the left side of the heart); from a nonbacterial thrombus 29 times

(6 from the ventricular wall; 14 from the proximal aorta, aortic valve or left atrium; 3 from the stem of a main coronary artery, 4 were paradoxical and arose from a pelvic vein; and 2 arose from the lung); and in 1 instance each from a caseous mass in the lung (Medlar, 1935), a calcareous mass whose source was not stated, and from a calcific mass detached from the aorta (Moragues *et al.*, 1950).

The immediate prognosis of embolism of a coronary artery or one of its larger branches is poor but, if the patient survives the initial effects of the embolism, the chances are good that the recovery will be complete. The diagnosis may be made during life if the patient has bacterial endocarditis or thrombophlebitis and develops symptoms of coronary occlusion. In bacterial endocarditis, emboli commonly occlude small branches of the coronary arteries.



Figure VIII-44. Recent thrombosis of left circumflex artery with embolism into more distal portion of the vessel. Fresh infarction and rupture of left ventricle. (WCGH, 46 A 64.)

de Navasquez (1939) examined serial sections of successive blocks cut from the left ventricular wall and septum in 20 unselected cases of *Streptococcus viridans* endocarditis. He found evidence of embolism to small arteries in 19 of the 20 hearts. In 16, sharply defined masses were found within the lumen of an artery and in 19, foci of polymorphonuclear leukocytes, with or without necrosis of adjacent myocardial cells, were found in the myocardium. In no instance, however, were bacteria demonstrable in these lesions. Saphir (1935) found small organizing myocardial infarcts in 28 of 35 unselected cases of subacute bacterial endocarditis. These small emboli produce no symptoms unless they are numerous, when they may seriously impair cardiac efficiency. Coronary embolism of bland thrombi is rare, of bacterial vegetations, common.

Paradoxical Coronary Embolism. Only a few cases of paradoxical or crossed coronary embolism have been reported. The occurrence of paradoxical embolism requires patency of the atrial or ventricular septum and a right-to-left shunt such as is produced when pressure in the right atrium or ventricle exceeds that in the corresponding left chamber. An increase in pressure of the right side with development of acute cor pulmonale often follows massive or recurrent pulmonary infarction and may set the stage for crossed embolism.

In all the following instances, a patent foramen ovale was present. The patient of Wolf and White (1926, Case 11) was a woman with carcinoma of the ovaries who had pelvic venous thrombosis and embolism of the patent foramen ovale and the descending branch of the left coronary artery. The patient of Thompson and Evans (1930) had a malignant teratoma involving both testes. Portions of the neoplasm metastasized by way of the veins to the right atrium and were carried through the patent foramen ovale into the left ventricle and both coronary arteries. In Saphir's patient (1933, Case 1), a thrombus in a femoral vein was carried to the left anterior descending coronary artery. The sudden death of the patient was attributed to lack of development of coronary anastomoses because of his relatively young age (35 years) and his freedom from coronary atherosclerosis. A similar case in which the embolus arose in a femoral vein was reported by Jacobi and associates (1934).

Air Embolism of Coronary Artery. In ex-

periments on guinea pigs, in which bronchovascular fistulas were produced, with entrance of air into the pulmonary veins, Rukstinat and LeCount (1923) were able to demonstrate air in the coronary arteries in all animals. In fatal cases, death was abrupt; some animals showed focal microscopic hemorrhages in the myocardium; in other animals, no focal lesions were present.

Rukstinat (1931) injected air into the coronary arteries of dogs. When 15 to 20 ml. was injected rapidly, death ensued within 1 to 4 minutes, but if the injection occupied 40 to 50 seconds, the cardiac disturbance was slight and the animal recovered. A number of instances of fatal air embolism (Lucas, 1936; Hall, 1937; Schattenberg and Ziskind, 1939) have occurred in refilling an old pneumothorax in which air has entered a pulmonary vein, and air emboli have been found in the cerebral vessels, and in the coronary arteries with or without hemorrhagic areas in the myocardium. A similar accident may follow thoracentesis or thoracic operations (Heller *et al.*, 1947). Rösle (1947) stated that in fliers, and in victims of explosion in the air or under water, there are sudden changes in the atmospheric and intra-alveolar pressures, with rupture of the pulmonary capillaries and entrance of air into the pulmonary capillaries or veins, air thus reaching the left side of the heart and coronary arteries. Air embolism to the brain may result in unconsciousness while air embolism to the coronary arteries may result in sudden death.

Durant and associates (1947, 1949) have reviewed the literature on air embolism. They believed that most cases of serious "pleural shock" in reality represent air embolism. They distinguished between pulmonary (venous) air embolism and arterial air embolism, depending on the site of entrance of air. In the pulmonary form, air enters one of the systemic veins and is carried to the right side of the heart and pulmonary circulation. In the arterial form, air enters a pulmonary vein and is carried to the left side of the heart and then to the systemic arteries. In the pulmonary form, should the heart possess a patency of the interatrial septum, as of the foramen ovale, paradoxical air embolism may result. In pulmonary air embolism, death results from circulatory obstruction because of an air trap

in the right ventricular outflow tract. The amount of air necessary to cause death is relatively large, being 150 ml. or more. In arterial air embolism, a relatively small amount of air is necessary. Involvement of the coronary arteries is believed to be a factor in causing death.

Durant and associates (1949) demonstrated that the injection of 0.5 to 1 ml. of air into the coronary arteries of dogs, or of 5 to 10 ml. of air into the left atrium or pulmonary veins produced ischemia of the myocardium in areas supplied by the involved vessels. The ischemia was also indicated by electrocardiogram and was demonstrable grossly. Two dogs survived injection of 5 ml. of air into the left atrium and two dogs died following injection of 10 ml. of air. These workers found that the vascular obstruction may be transient, the air being rapidly absorbed, but that the ischemia may persist despite the disappearance of air bubbles from the lumen of the coronary arteries.

Fat Embolism. In fat embolism following trauma, Warthin (1913) called attention to possible damage to the heart. He pointed out the macroscopic presence of fat in subepicardial vessels, miliary hemorrhages and patches of fatty degeneration in the heart muscle, and in microscopic sections, fat-emboli in numerous blood vessels, and large droplets in the heart muscle in the immediate neighborhood of these vessels. Some of the fat in the muscle fibers apparently is derived from the neighboring fat-emboli. The fatty material is transferred from the venous to the arterial side by passing through the pulmonary capillaries. This transfer is said to be favored by subsequent trauma or jarring of the patient (Vance, 1931). The fat is distributed to the capillaries of the entire circulatory area but the principal effects of the embolism appear to be manifested in the brain, heart, kidneys and lungs. Plugging of the capillaries and arterioles results in focal anoxia and minute infarcts with petechial hemorrhages. In the heart the hemorrhages may be minute and in the form of streaks in the ventricular muscle, while the adjacent muscle may reveal numerous microscopic fatty globules.

Szurek and Czaja (1933) injected 1 to 2 ml. of oil obtained from canine adipose tissue into the descending branch of the coronary artery of dogs and exsanguinated the animals after various periods from 6 hours to 30 days. They found sausage-shaped fatty emboli causing occlusion of the capillaries. Some oil was still present after 30 days. Permanent blocking by oil was followed by focal infarction. In the pulmonary form of fat embolism, Warren (1946) gave the location of petechial hemorrhages as pericardium, conjunctivae and pleurae in that order of frequency. He stated that fat may pass the pulmonary circuit or go through a patent foramen ovale, but doubted that embolic involvement of the coronary arteries was a significant factor in producing death. In cases in which the coronaries were involved, other organs were severely affected. In 8 of 100 cases of fat embolism he found a significant degree of coronary involvement. Harman and Ragaz (1950) produced fat embolism in rabbits by the intravenous injection of homologous fat. In animals dying immediately, death was ascribed to massive plugging of the pulmonary vessels. In animals that survived the injections by several hours, the principal changes were pulmonary edema, focal necrosis in the heart and liver, and scattered petechiae. The changes in the heart included petechial hemorrhages of the pericardium and beneath the endocardium of the left ventricle, and presence of grossly perceptible fat globules in the dilated right ventricle; and microscopically, hyperemia of the myocardium and focal necrosis with infiltration of monocytes and neutrophilic polymorphonuclear leukocytes. The focal necrosis was attributed to embolism of small vessels by fat.

Dissecting Aneurysm of Coronary Artery. Only a few instances of dissecting aneurysm of the coronary arteries have been reported.

Wainwright (1944) described an instance of dissecting aneurysm of the aorta which extended to produce dissection of the left coronary artery and its anterior descending branch and consequent occlusion of the lumen of the vessel by the pressure of the hematoma within its walls, and myocardial infarction. He believed that the rarity of obstruction of the coronary artery from this cause is to be explained by the proximity of the coronary orifices to the reflection of the pericardium on the aorta, rupture usually occurring into the pericardial sac before the dissection can extend widely in the walls of the coronary arteries. The anatomic relations of the orifices in the sinus

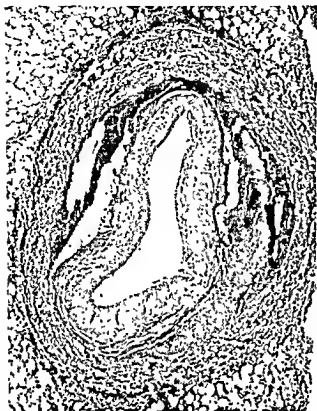


Figure VIII-45 Dissecting hemorrhage in outer portion of media of right coronary artery, which caused sudden death in a 41-year-old previously healthy woman, apparently as a result of periarthritis nodosa. Case reported by Ahronheim and Wagman (*Arch Path.*, 69:19-23, 1959). X 20. (WCGH, 57 P 662.)

of Valsalva are also thought to afford protection against dissection of the coronary arterial walls. Whittaker and Sheehan (1954) reported a case of Marfan's syndrome in which a dissecting aortic aneurysm encircled the right coronary artery.

We have observed a case referred by Dr. J. H. Ahronheim of Jackson, Michigan, of a dissecting aneurysm in the ramus interventricularis posterior of the right coronary artery which caused sudden death in a 41-year-old woman (Figure VIII-45). The nature of the periaortitis infiltrate suggested polyarteritis nodosa, but this lesion was not found in any other artery examined at autopsy.

Coronary Arteritis without Aneurysmal Formation. Barnett and Zimmerman (1947) reported an instance of thromboarteritis of the coronary artery in a 48-year-old man with septicemia caused by *Salmonella choleraesuis*. The renal and hepatic arteries were similarly involved. The lesions were judged to represent those of true arteritis rather than manifestations of polyarteritis nodosa.

Compression of Coronary Artery by Neoplasm. Peppard and Larson (1933) reported occurrence of metastatic carcinoma from the breast to the epicardium with compression of the lumen of both coronaries but especially the left. The myocardium was soft but not infarcted.

Obstruction of Coronary Sinus. Grant and Jones (1928) encountered at autopsy in a 28-year-old man a fibrous diaphragm which occluded the lumen of the coronary sinus in its midportion. The fibrous tissue appeared to be the result of an old thrombus of the sinus, rather than a congenital malformation. In this case it is of interest to note that the obstruction apparently caused no interference with coronary circulation and did not produce obvious dilatation of the tributary veins, thus indicating the functional efficiency of the venous anastomoses present on the surface of the heart.

In experiments on dogs, Lorber and Greenberg (1944) demonstrated that gradual occlusion of the coronary sinus did not increase the coronary arterial bed but rather reduced it. Warner and Dauphinee (1936) encountered complete occlusion of the coronary sinus by a thrombus in a 45-year-old man with widespread migratory phlebitis and carcinoma of the bronchus. Clinically the patient had severe dyspnea and paroxysmal tachycardia, but no cardiac pain. The diagnosis of phlebitis with thrombosis was made during life, after excision of a superficial vein. McAllister and Leighninger (1950) produced infarction of the right ventricle in dogs by ligating both the coronary sinus and the anterior cardiac veins, indicating that the intramural venous drainage-system (thebesian vessels) was incapable of accommodating the inflow of oxygenated blood to this area.

Miscellaneous Lesions

Coronary Arteriosclerosis. Jacobson and Raokin (1950) reported sclerosis of the coronary arterioles, without significant atherosclerosis of larger coronary arteries, in a 70-year-old man. He encountered only 2 such cases in the literature, one patient was a woman 46 years of age and the other, a man 41 years old. The lesion affected arterioles having an external diameter up to 350 micra, and was

characterized by marked hyalinization and hypertrophy of the media; the thickness of the wall was equal to or twice the diameter of the lumen. There was no associated hypertension or cardiac hypertrophy, obstruction of the coronary arteries, or arteriolar disease of other organs including kidney.

Aneurysm of the Coronary Arteries. Polyarteritis nodosa (Figures VIII-46 and 47) is the commonest cause of aneurysm of the coronary arteries. Although polyarteritis nodosa of coronary arteries is usually part of a generalized arteritis, its occurrence without involvement of other organs has been described in infants (Sinclair and Nitsch, 1949).

Fraenkel (1917) described an aneurysm of the left coronary artery immediately beyond the orifice, in a 20-year-old soldier, who had sustained an injury six months previously. The aneurysmal vessel was filled with a red thrombus and was associated with aneurysmal bulging of the apical half of the left ventricle and with a mural endocardial thrombus. Fraenkel thought that a trau-

matic origin was likely. A single aneurysm of the coronary is usually situated immediately distal to the orifice, within the first inch of the vessel; multiple aneurysms are usually located at points of division of the artery (Packard and Wechsler, 1929).

Scott (1948) reviewed the literature on aneurysms of the coronary arteries exclusive of those proved to have resulted from polyarteritis nodosa. He classified these aneurysms as localized, diffuse and dissecting. Of 47 localized aneurysms, 15 were regarded as congenital; 12, mycotic-embolic; 6, atherosclerotic, 6 syphilitic; 1, purely mycotic, 1, rheumatic, 2 probably caused by polyarteritis nodosa; and 4, unclassified. The left coronary artery only was involved in 27 instances, the right artery only in 11, and both arteries in 6, and in 3 instances the affected artery was not named. In 36 instances a single aneurysm was present; in 8, multiple aneurysms; and in 3 instances no statement is made, but presumably a single aneurysm was present. Fourteen of the 15 instances of congenital aneurysm were encountered in males. In the atherosclerotic aneurysm, the internal elastic layer may be destroyed

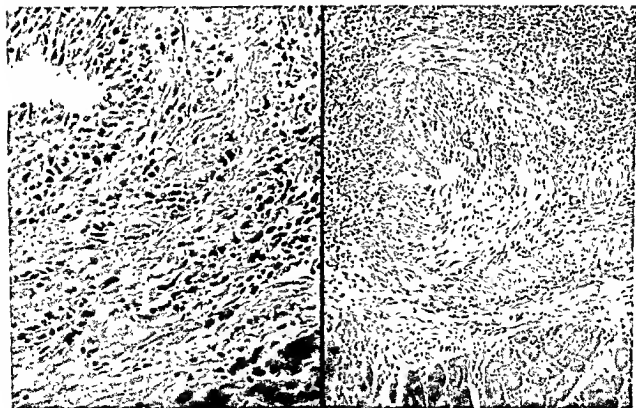


Figure VIII-46 (left). Periarthritis nodosa of branch of left coronary artery. Note necrosis of media of vessel and inflammation within walls and peripheral to vessel. X 250. (WCGH, 58 P 283-8.)

Figure VIII-47 (right). Periarthritis nodosa of branch of coronary artery, showing obliterating fibrosing endarteritis and heavy perivascular infiltrations. X 110. (WCGH, 58 P 283-4.)



Figure VIII-48. Vanees ("blood cysts" or hemangioma) of mitral valve in 8-week-old boy. X 100. (A 253 BA, University of Michigan, WCGH, 58 P 479.)

at the site of atheromatous plaques. The *mycotic-embolic aneurysms* are usually secondary to bacterial endocarditis of the mitral or aortic valve. The commonest causes of death in the localized aneurysms were rupture (in about 50 per cent of cases), coronary thrombosis, and congestive heart failure. Scott reported the occurrence in a man of 84 of *multiple aneurysms* involving both coronaries, the largest aneurysm measuring 10 by 8 by 8 cm. A roentgenogram revealed a large globular shadow to the right of the heart and displacement of the esophagus to the left, while the electrocardiogram revealed a shifting pacer-maker. The patient, however, had had no cardiac symptoms. Scott also found 5 reports of diffuse aneurysm and 1 of dissecting aneurysm. All of the *diffuse aneurysms* were thought to be congenital, 4 of them involved the right coronary and 1, the left circumflex. In a report of 17 cases of polyarteritis nodosa with autopsy, Griffith and Vural (1951) found 7 which showed evidence of polyarteritis nodosa in the heart. Of 3 myocardial infarctions found in this series, only 1 was thought to have been caused by polyarteritis nodosa.

In the *mycotic-embolic aneurysms* the lumen contains the infected embolic material. The infection first involves the intima and then spreads either directly to the media and adventitia or to the adventitia by way of the vasa vasorum and

finally to the media. There is inflammatory reaction with infiltration of polymorphonuclear leukocytes and lymphocytes and destruction of the internal elastic lamina, fibroblastic proliferation, later destruction of muscular tissue and finally hemorrhage in the adventitia and surrounding tissue. Occlusion of the lumen of a coronary artery by embolus from vegetative endocarditis may cause myocardial infarction. Pure mycotic aneurysms are secondary to septicemia, as from osteomyelitis. In view of the great rarity of the so-called *atherosclerotic aneurysms*, the atherosclerotic process may be but one factor in the production of these aneurysms. In addition to the severe atherosclerosis, the vessel at the site of an atheromatous plaque may have undergone destruction of the internal elastic lamina and atrophy of the media.

Edwards (1958) has pointed out that, in a number of instances of so-called congenital aneurysm of the coronary artery, the artery communicates with the circulation of the right side of the heart (including the coronary sinus or one of its tributary veins, the right atrium or ventricle, or the pulmonary trunk), or with the left atrium or ventricle. In such instances, the artery is in effect part of an arteriovenous communication, and the flow of blood is from the systemic arterial system to the venous side, with resulting dilatation and tortuosity of the artery. (See also page 429.)

Anoxic Necrosis of Coronary Arteries in the Newborn. Crimewald (1949) encountered at autopsy medial necrosis of the coronary arteries in 21 stillborn and newborn infants or in 9.5 per cent of those up to 3 days of age who showed signs of asphyxia, including focal hemorrhages in various organs. The areas of necrosis consisted of masses of eosinophilic material, chiefly in the outer portion of the media, which were focal or surrounded most or all of the vessel. Some of these lesions enclosed cavities containing granular debris and occasional erythrocytes. The lesion appeared to progress from the adventitia toward the intima and suggested impairment of the nutrition of the vessel wall, derived from the adventitia.

Rupture of Coronary Artery. Olcott (1931) reported a case of rupture of a coronary artery and found 30 cases in the literature. Fifteen of the 31 cases were associated with coronary aneurysm, and 16 were not. In 14 the *etiology* was thought to be atherosclerosis; in 5, an

infection (embolic); in 2, syphilis; and in 10, the cause was undetermined.

The average age of the patients of the infectious group was 19 years; of the syphilitic group, 46, and of the arteriosclerotic group, 65. The vessels involved and the frequency of involvement were as follows. left coronary artery, 11 times; the right, 8, both vessels, 3; and in 9 instances the vessel affected was not stated. The patients were males in 19 cases, females in 11, and in one instance the sex was not stated. Bradbury (1942) reported survival of a woman (aged 75, alive and comfortable at the time of the report) for 32 years following severance, by a stab wound, and ligation of the mid-portion of the anterior descending branch of the left coronary artery.

Coronary Arteriovenous Fistula. The term "coronary arteriovenous fistula" refers to a communication between a coronary artery and a vascular structure by means of which blood is shunted into a channel without first passing through capillaries. Such a fistula results in dilatation of the coronary artery and generally is aneurysmal in appearance.

Steinberg and associates (1958) reported a case and reviewed the world's literature. He found a total of 21 cases, 13 with autopsy. He listed the following structures which communicated with a coronary artery: right coronary artery with pulmonary trunk or a pulmonary artery (3 cases); coronary sinus (3); coronary vein (2), right atrium (2); left coronary artery with pulmonary trunk or a pulmonary artery (2), coronary sinus (2); coronary vein (1); right ventricle (3);

left atrium (1); not specified (3). The authors attributed the fistula to either embryonic arrest of normal development of coronary vessels or to anomalous origin of a coronary artery with a left-to-right shunt of blood flow.

Thrombosis of Coronary Vein. Lake (1958) reported antemortem thrombosis of a coronary vein with fresh hemorrhage in the myocardium ($\frac{1}{2}$ by $\frac{1}{4}$ inch) surrounding the distal portion of the anterior descending coronary artery, in a healthy man who died 14 hours after he had collapsed while engaged in heavy labor on a hot day. Hemorrhage was present in the wall of the distended vein and in the adjacent myocardium but the coronary arteries showed no histologic changes. A section from the apex at a distance from the gross hemorrhage revealed marked infiltration of polymorphonuclear leukocytes. The author cited from the literature 4 other cases of thrombosis of a coronary vein.

Varices of the Heart. A common site for varices of the coronary system is the right atrium at the inferior or posterior border of the foramen ovale (Schulz, 1930). Other sites include papillary muscles, a leaflet of the tricuspid or mitral valve (Figure VIII-48) and the subepicardial fat. Varices are formed on the basis of a congenital underdevelopment of the venous wall. The lower pressure within the right atrial chamber may also be a factor in their formation. In most instances, varices have been encountered in aged persons and have had no clinical significance.

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Rheumatic Disease of the Heart

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Historical

ACCORDING TO WELLS (1812), Pitcairn, about the year 1788, first remarked that persons subject to rheumatism were "attacked more frequently than others, with symptoms of an organic disease of the heart." Subsequent experience confirmed the truth of this observation and he concluded that these two diseases often depended on a common cause, and called the latter disease "rheumatism of the heart." He communicated his observation to several of his friends, and to his pupils at St. Bartholomew's Hospital to which he was then physician, but no notice was taken of his remark in any book before it appeared in the second edition of Baillie's *Morbid Anatomy*, published in 1797.

Jenner was also among the first to associate rheumatic fever with heart disease. According to records of the Fleece Medical Society, of which Jenner was a member, on July 29, 1789, "Mr. Edward Jenner favored the society with remarks on a disease of the heart following acute rheumatism illustrated by dissections." A classic account of the association of acute articular rheumatism and heart disease was written by Jean Bouillaud in 1835.

In his famous law of coincidence, he stated (1840): "In the great majority of cases of diffuse articular rheumatism with fever there exists in a variable degree a rheumatism of the serofibrous tissue of the heart. The coincidence is the rule, and the noncoincidence the exception."

Baillie in 1793 first described the acute form of pericarditis with exudation of "coagulable

lymph" from the blood vessels in the pericardium and fluid in the pericardial cavity. Pulteney in 1761 had reported a case of adherent pericardium in a young man who had suffered from fever and arthritis 2 years previously.

In 1835 Sir Thomas Watson recognized rheumatic fever as essentially a disease of childhood.

"One law respecting the connection between the cardiac and the arthritis symptoms may be stated with confidence, namely, that the younger the patient is who suffers acute rheumatism (and I have seen it as early as the third or fourth year) the more likely will he be to have rheumatic carditis. The chance of this combination appears to diminish after puberty as life advances."

MacLagan in 1881 emphasized the specific action of the salicylic group of drugs. Salicylic acid was the first of these to be used in the treatment of acute arthritis, but because of its irritant action it was supplanted by sodium salicylate. Cheadle (1889), in his lectures before the Harveian Society of London in 1888, presented a classical description of rheumatism in childhood to which little can be added at the present time.

It was not until the latter part of the nineteenth century that rheumatic myocarditis was recognized. The myocardial lesions were described by several investigators (Goodhart, 1879; Romberg, 1894) before the specificity of the interstitial myocardial lesion was established by Aschoff in 1905.

In 1887 the microbic origin of rheumatic fever was investigated by Mantle. In the next 20 years the names of Geipel (1905), Poynton (1899) and Paine (1900), and Goombs (1907) were associated with further discussion of the pathology and etiology of rheumatic disease. In the past 40 years, investigators have been engaged in bacteriologic and immunologic studies in unsuccessful efforts to determine the etiologic agent of the disease. The majority of these studies have centered about the possible etiologic significance of micro-organisms of the genus *Streptococcus*.

The main contribution to our knowledge of rheumatic fever during the past 30 years has been in the field of pathology.

The studies of Klotz (1912), Pappenheimer and Von Glahn (1924, 1927), MacCallum (1924), Klinge (1933), Swift (1924, 1929, 1947), Gross (1935a, b), Clawson (1925, 1929, 1938, 1940a, b, 1941, 1945), and others clearly demonstrate that rheumatic fever is a systemic disease, probably an infectious disease with lesions throughout the body. Most important of these is the lesion of the cardiovascular structures.

Prevalence

Rheumatic disease of the heart ranks with coronary and hypertensive heart disease as one of the most common and serious types of disease of the heart. It is especially important and serious because it is particularly a disease of youth, killing or crippling many children and young adults.

Surveys of school children of some of the large cities of the United States (Paul, 1928, 1945; Paul *et al.*, 1934) indicate an incidence of rheumatic heart disease of approximately 3 to 14 cases per 1000. Glover (1930) in England found that in the age group 10 to 15 years, rheumatic fever causes 5.4 per cent of all deaths, and heart disease (80 per cent of which was due to rheumatic fever at this age), 10.8 per cent or a total of 16.2 per cent. This is four-fifths as much as all forms of tuberculosis and more than twice as much as measles, scarlet fever and diphtheria combined. In the United States rheumatic fever with heart disease is the leading cause of death in children 10 to 15 years of age. At ages 15 to 24 years it is second only to tuberculosis. It has been estimated that, among persons less than 20 years of age, for each death from the combined causes of pertussis, diphtheria and poliomyelitis there are 50 deaths resulting from rheumatic disease of the heart (Mustard, 1947).

Natural History

It is now generally recognized that rheumatic fever is a chronic inflammatory disease. Cohn and Lingg (1943), in a statistical study of 3,129 patients, noted recurrences in 75 per cent during an average period of 13 years after the onset of the illness.

The largest incidence of recurrence was in patients between the ages of 5 and 14 years. According to these authors, a sharp decline in recurrences takes place at the age of 12 years; in-

volvement of the heart can be recognized in approximately 65 per cent of patients during the course of rheumatic fever in childhood; and the earlier the age at onset, the greater is the chance that infection will be severe during the next few years.

In a 10-year study of 1000 cases of rheumatic fever, Jones and Bland (1942) found that 65.8 per cent had some degree of rheumatic heart disease while 34.2 per cent had no detectable heart disease at the termination of their first attack. In this latter group of 342 patients, about 72 per cent were free of rheumatic heart disease at the end of 10 years. Two-thirds of those who later had rheumatic heart disease had a recognizable recurrent episode of rheumatic fever. Of the 658 patients who had rheumatic heart disease at the end of their initial attack of rheumatic fever, the cardiac condition of 22 per cent improved, that of 27 per cent was unchanged, and that of 51 per cent had progressed at the end of 10 years. The occurrence of repeated attacks of rheumatic fever was the chief feature which determined whether rheumatic heart disease would progress or regress. In 75 (7.5 per cent of the entire series) clinical evidence of rheumatic heart disease disappeared, while in 68 (8.8 per cent of the total series) it decreased. At the end of 10 years the status of the heart disease in these 1000 patients was as follows: 313 (31.3 per cent) had no detectable heart disease; 470 (47 per cent) had some degree of rheumatic heart disease; 203 (20.3 per cent) were dead, most of them as the result of recurrent rheumatic fever; and concerning 14 (1.4 per cent) the follow-up data were too inadequate to be of value.

Bland and Jones (1951) also reported the course of these 1000 patients with rheumatic fever over a period of 20 years. Of 301 who died, 40 per cent had had extensive rheumatic heart disease when first seen. Rheumatic fever and rheumatic heart disease were responsible for most deaths. Ten per cent of the 301 patients died of bacterial endocarditis. The serious prognostic features were: a history of a severe initial attack of rheumatic fever, great enlargement of the heart, and development of congestive failure early in the disease. Of the patients who had no detectable rheumatic heart disease at the time of their initial illness, 44 per cent developed rheumatic heart disease during the 20-year period. However, a large majority of patients who survived 20 years from the onset of rheumatic fever had little or no restriction of physical activity.

According to Cohn and Lingg (1943), the duration or life expectancy differs with the age at onset.

When the disease begins in childhood, 69 per cent survive childhood, 35 per cent survive adolescence, 18 per cent reach the age of 30 years, and 5 per cent live beyond the age of 45 years. When the disease begins in adolescence, 85 per cent survive this age period, 55 per cent reach the age of 30, and 21 per cent the age of 46 or more. When the onset is in the third decade, 23 per cent survive the age of 45 years, and when the onset is after 30, 44 per cent survive the age 45.

Somewhat similar findings have been reported by Ash (1948) in a study of 537 children in Philadelphia observed for 10 years after the onset of rheumatic infection. At termination of the initial attack, 59.2 per cent showed evidence of the presence of rheumatic heart disease. Of 219 patients with no clinical evidence of heart disease at termination of their first attack, 78.7 per cent still showed no evidence of heart disease 10 years after onset. Only 5 per cent of this group who did not have heart disease clinically at the termination of their first attack had died of rheumatic infection or bacterial endocarditis. Of 318 patients who had rheumatic heart disease after the initial episode of rheumatic fever, 30 (9.4 per cent) showed disappearance of signs of cardiac involvement and 42.1 per cent had died of rheumatic infection or bacterial endocarditis. Of the group who had heart disease after the initial episode of rheumatic fever, 60.3 per cent of those living 10 years after the attack were leading a normal existence with little or no limitation of activity. Of the whole group, at the end of 10 years, 24.4 per cent had died of rheumatic infection in comparison with a death rate of 42 per cent among those diagnosed as having rheumatic heart disease at onset.

Wilson and Lubschez (1948) reviewed the records of 1,042 children who were under observation for a period of 30 years. Eighty-nine per cent of the patients were seen at the time of death or at the end of the study. The over-all death rate was 14.7 per 1,000 per year. The highest death rates occurred be-

tween the ages of 1 and 4 years (33.2 per thousand) and 10 to 14 years (16.3 per thousand). An affected child has 4 chances out of 5 to survive 15 years after the onset of the disease, 3 chances out of 4 to survive 20 years after onset, and 2 chances out of 3 to survive 30 years after onset.

Cause of Death in Rheumatic Fever. In the study by Jones and Bland (1942), of 1,000 patients with rheumatic fever, 10 years after the initial attack, one-fifth (203) had died, most of them (83 per cent) after repeated episodes of rheumatic fever. Sixteen (8 per cent) of the deaths were caused by bacterial endocarditis superimposed on the previous rheumatic valvular disease. Nineteen persons died as the result of diseases or accidents unrelated to rheumatic fever or rheumatic heart disease. Among 226 deaths analyzed by Wilson and Lubschez (1948), 75 per cent resulted from rheumatic disease of the heart and 10 per cent from subacute bacterial endocarditis. In the study of the first 10 years of rheumatic infection in 588 children, Ash (1948) found that one-fourth (131) had died from rheumatic infection, 2 per cent (12) from bacterial endocarditis and 1.4 per cent (8) from unknown or unrelated causes. On rare occasions sudden death occurs as a result of rheumatic carditis (Hamilton *et al.*, 1948; Moritz, 1948).

Wallach and associates (1956), in a study of 509 patients with rheumatic heart disease, concluded that with increasing age rheumatic heart disease is more often a relatively inactive incidental lesion and that its rôle as a cause of death becomes less significant.

Yet rheumatic changes of the heart valves were not rare, having been encountered in 59 per cent of a series of 5676 consecutive autopsies. Old rheumatic heart disease was a significant cause of death, particularly in the middle decades, while active rheumatic fever was usually significant only in the early decades of life.

Etiology

PREDISPOSING CAUSES

Age. Rheumatic fever may begin at any age but it usually begins in childhood, especially between the ages of 4 and 10 years.

Logue and Hurst (1952) reported 26 cases of rheumatic fever occurring at or before 5 years of age. In a study of 1042 children Wilson and Lubschez (1948) found that the mean age at onset was 6.5 years. The disease was observed in the great majority of cases between the ages of 4 and 50 years and rarely did it begin before the age of 2 years. An example of intra-uterine rheumatic heart disease was reported by Kissane and Koons (1933); Schwarz (1932) reported rheumatic heart disease in an infant aged 17 months. Of all instances of rheumatic cardiac disease, two-thirds begin in childhood, and one-third at later age periods. Over one-half (56 per cent) occur in adolescence. Only 16 per cent were 45 years or older, and only 3 per cent were first affected after the age of 45 (Cohn and Lingg, 1943). The occurrence of the first attack of rheumatic fever relatively late in life has been emphasized by Ferris and Myers (1935) who reported 6 cases in which the first attack occurred after the age of 60 years. The course of the disease is similar to that in younger persons except that the manifestations of the joints are possibly less intense and more persistent. Rogers and Robbins (1947) pointed out that the initial as well as recurrent attacks of rheumatic fever in the later years of life may arise in the complete absence of characteristic clinical signs, progressing insidiously to acute cardiac decompensation and death.

Although rheumatic fever usually begins in childhood, it should be emphasized that most rheumatic cardiac lesions are observed at necropsy in the older age groups. Most, but not all, of these lesions in older persons are quiescent or healed.

In a chronic disease hospital, Kaufman and Polakoff (1950) found 50 instances of rheumatic heart disease among 263 consecutive necropsies. Twenty-eight per cent of the group with rheumatic heart disease were between the ages of 40 and 50, and 72 per cent between 50 and 81 years. In 16 of the 50 cases (32 per cent) clinical evidence of activity of the disease was found while the patients were on the wards, and evidence of this activity was found at necropsy.

These figures indicate that heart disease of rheumatic type also occurs in the later years of life.

Sex. In various reported series there is a

slightly higher incidence of the disease among girls than among boys.

In a series of 696 patients reported by Wilson (1940), 387 were girls and 309 were boys; the difference in incidence was not significant.

Climate. Rheumatic fever is especially prevalent in the temperate zones, is less frequent in the subtropics and is rarely seen in the West Indies (Swift, 1924, 1929, 1947).

In Boston at the Peter Bent Brigham Hospital, the incidence of rheumatic fever in the years 1914 to 1923 was 1.85 per cent of all medical admissions, the clinical incidence of mitral stenosis was 3.89 per cent, and the incidence of stenosis of the mitral orifice at necropsy was 4.68 per cent, while in New Orleans at the Charity Hospital those percentages from 1916 to 1923 were 0.03, 0.08 and 0.23, respectively (White, 1951). According to Clarke (1930), there is about 15 times as much rheumatic fever in the temperate climates as in the tropics. Büngeler (1942), however, stated that rheumatic fever is just as frequent in the tropics as elsewhere.

Involvement of the joints is said to be relatively mild in the southern part of the United States, whereas carditis may be severe. The incidence of carditis in the South, however, parallels the decreased incidence of rheumatic fever (Nichol, 1936). Classic polyarthritic manifestations are said to be rare in the central states, whereas mitral stenosis is common. These observations indicate a climatic influence on both incidence and clinical manifestations (Swift, 1924, 1929, 1947). Jones and his associates (1937) advised caution, however, with regard to the unquestionable value of transportation of patients with rheumatic fever to a subtropical climate.

Seasonal Incidence. Rheumatic fever is usually prevalent in localities subject to cold and rain and to sudden wide fluctuations of temperature, irrespective of geographic location. In this country recurrences are more frequent in winter and spring than in the summer and fall.

Economic and Social Factors. It is generally thought that rheumatic fever is more common among the poor, although its occurrence in the higher economic levels of society is not infrequent.

Coburn (1931) found a ratio of 20:1 in New York City. In New Haven, Connecticut, Paul and associates (1934) found that 5 per cent of the school children in a poorer section of the city had rheumatic heart disease. This was one and one-half times the incidence of the disease in a public school in a better section of the city, and 8 times that in a neighboring private school. Wilson and Lubshez (1948), however, found that the majority of the children with rheumatic fever surveyed in New York City came from moderately well-to-do homes of the industrial laboring class of the city.

The British Medical Research Council (1927) did not find the economic factor to be of prime importance in the occurrence of the disease.

Nutrition. A number of studies have suggested that poor nutrition is a more important factor predisposing to the development of rheumatic fever than economic status. Vitamin C deficiency (Rinehart, 1935), high carbohydrate and low protein diets (Weston, 1948) have been regarded as important. It also has been demonstrated that giving patients a nutritious diet tends to prevent recurrences (Coburn and Moore, 1943).

Familial Epidemiology. Wilson's (1940) observation revealed a significantly greater prevalence of rheumatic fever among families in which parents had had rheumatic fever than among families in the same environmental group in which the parents had not had it. The data obtained by her study do not support the view that rheumatic activity is passed from one member to another member in the family. On the basis of genetic analysis, hereditary susceptibility underlies the familial incidence of the disease, although it probably is not the sole condition essential for its development (Rosenblum and Rosenblum, 1941). Aside from its occurrence in families, epidemics of rheumatic fever have been recorded in dwellings occupied by more than one family, and in military camps, schools and communities (Paul, 1945).

EXCITING CAUSES

Acute rheumatic fever has long been regarded by many authorities as an infectious disease. The etiologic agent responsible for

the disease has been a subject of much controversy for many years.

Virus. Supportive evidence that a filtrable virus is the etiologic agent of rheumatic fever was presented by Schlesinger, Signy and Amies in 1935. They were able to obtain elementary bodies, by centrifugation at high speed, of the pleural and pericardial exudates of patients with rheumatic fever. These elementary bodies were agglutinated only by the serum of patients who had active rheumatic fever.

Eagles and associates (1937) also obtained suspensions of particles similar to the elementary bodies of virus infections from a variety of materials from patients who had acute rheumatic fever, rheumatoid arthritis, and chorea. Suspensions of these particles were agglutinated by the sera of patients who had the same disease as the patient from whom the material for the suspension was obtained. Control suspensions were not agglutinated by any of the rheumatic sera. They were not able to produce rheumatic lesions by inoculation of the virus-like bodies into monkeys. MacNeal and associates (1946) reported that they had grown on chick embryos an agent from the blood of a child with rheumatic fever. Mule (1953) stated that he had observed under the electron microscope elementary bodies in erythrocytes of patients with rheumatic fever.

However, the results of studies on the viral etiology of rheumatic fever have not been confirmed.

Bacteria. Poynton and Paine (1913) isolated a small diplococcus from the heart's blood and other tissues in 8 cases of rheumatic fever in 1900. During the last 30 years the view that rheumatic fever is a manifestation of streptococcal infection has been gaining ground.

Some investigators have held that it is caused by a specific strain of streptococci (nonhemolytic, Birkhaug, 1928, *Streptococcus cardio-arthritidis*, Small, 1927). Zinsser (1931) and, at one time, Swift (1924) asserted that a variety of different strains of nonhemolytic streptococci were responsible. Clawson (1925) and Cecil and associates (1929) used special techniques and obtained a relatively high percentage of positive cultures from rheumatic individuals. Clawson found streptococci in more than 50 per cent of persons with

acute rheumatic fever, but large amounts of blood had to be used and the organisms rarely grew in less than 5 days. The organisms did not belong to a specific group but produced a green color and had rather low virulence. Clawson (1938) and other workers have succeeded in producing subcutaneous nodules similar to those of rheumatic fever by the inoculation of animals with streptococci. Dawson (1943), Nye and Waxelbaum (1930), and others either did not confirm these findings or discounted their significance.

The study of Lichtman and Cross (1932) of 5283 consecutive blood cultures revealed that the incidence of recovery of nonhemolytic streptococci ranged from 4.0 to 15.5 per cent, with an average of about 6.0 per cent, in the following diseases: acute rheumatic fever with polyarthritis, chronic rheumatic heart disease, rheumatoid arthritis, aplastic anemia, pernicious anemia, leukemia, colitis, meningococcal meningitis, pyelitis, and pyelonephritis. Callow (1933) isolated green-producing streptococci and pleomorphic bacilli with equal frequency from the blood of patients with rheumatic fever and from the blood of patients with nonrheumatic diseases. Wilson (1940) found that 46 per cent of 67 children of the rheumatic series and 41 per cent of 91 children in the control series had bacteremia.

At present a majority of investigators seem to believe that organisms recovered from the blood of patients who have rheumatic fever are not of etiologic significance and probably represent transitory bacteremia.

The observations of Coburn (1931) have centered interest on hemolytic streptococci as one of the responsible agents for rheumatic fever. The concept that hemolytic streptococci are related in some undefined manner to rheumatic fever is now accepted by many investigators in this field.

The following facts have been listed by Spink (1948) as evidence in favor of this hypothesis: 1. Upper respiratory infections caused by group A hemolytic streptococci are frequently closely followed by rheumatic fever. In fact, epidemics of rheumatic fever have been associated with large numbers of cases of streptococcal respiratory disease. 2. Recurrent attacks of rheumatic fever are often preceded by streptococcal respiratory infections. 3. Patients who have active rheumatic fever exhibit certain immune responses characteristic of invasion of the tissues by hemolytic strep-

tococci, such as an increased titer in the serum of antistreptolysin, antifibrinolysin and anti-M precipitins. 4. Although the sulfonamides do not alter the course of rheumatic fever, carefully controlled studies indicate that the prophylactic use of these compounds will prevent the invasion of tissues by hemolytic streptococci and thereby reduce the incidence of recurrent attacks of rheumatic fever.

Evidence contrary to the widely accepted view, that infection with hemolytic streptococci is responsible for the genesis of rheumatic fever, has been collected by Wilson. Her studies indicate that the majority of recurrences in rheumatic children under observation were manifest in the absence of accepted bacteriologic and immunologic evidence of preceding streptococcal respiratory infection. Although most of the children suffered from repeated respiratory infections, rheumatic fever followed such episodes only infrequently. According to Wilson, little evidence has been presented to date in support of the hypothesis that respiratory infection caused by hemolytic streptococci is responsible for the initial attack of rheumatic fever. Investigations have been concerned mainly with the relationship of such infections to recurrences of rheumatic fever.

Hormones. Selye in 1946 was able to produce vascular lesions identical with those in periarteritis nodosa and hypertension, lesions like those of nephrosclerosis and sometimes of acute nephritis, and myocardial and articular lesions similar to those observed in acute rheumatic fever, by giving large doses of desoxycorticosterone acetate or anterior pituitary extracts. He postulated that the diseases of man which are thus imitated by overdosage of the hormone might arise as a result of an excessive production of endogenous salt-active corticoids. In this sense, these lesions would have to be interpreted as diseases of adaptation.

In support of this concept, he pointed out that fatigue, chills, traumatic injuries, and mental upset may cause the relapse of rheumatic fever from a quiescent to an acute febrile state. It is interesting in this connection that Hench and his co-workers (1949) have found that certain

clinical, biochemical and electrocardiographic features of rheumatoid arthritis and rheumatic fever have been improved by the daily intramuscular injection of either the adrenal cortical hormone, 17-hydroxy-11-dehydrocorticosterone (compound E) or the pituitary adrenocorticotrophic hormone (ACTH). This may indicate that a lack of certain hormones, rather than their overproduction, is a causative factor in these diseases.

PATHOGENESIS

Experimental. The question as to how any etiologic agent produces the morphologic and clinical picture of rheumatic fever has received considerable attention. The disease is believed to be an allergic response of tissues previously sensitized by a specific or a non-specific streptococcal infection.

This hypothesis was suggested by Meuzer (1902). Later it was re-introduced by Herry (1914) and received support from the experimental work of Faber (1915), Swift (1924, 1928, 1929, 1947), Klinge and Vaubel (1931), Zinsser (1931), Vaubel (1932), and Junghans (1934). Gross, Loewe and Eliasoph in 1929 and Bruun in 1940 repeated these experiments with only equivocal results and concluded that they had not reproduced a true analogue of the Aschoff nodule.

Numerous studies are on record of experimental attempts to reproduce rheumatic fever, rheumatic endocarditis and myocarditis. At first, attempts were made to reproduce the disease by introduction of streptococci into the body. Later efforts were made to reproduce rheumatic fever by changing the immune status of animals from a nonergic to a hyperergic condition by various means and particularly by introduction of hemolytic streptococci. More recent experimental work concerns especially the role of group A beta-hemolytic streptococci.

Rich and Gregory (1943) have been able to reproduce more closely the 5 supposedly pathognomonic features of acute rheumatic carditis. These have been listed as focal alterations of collagen, Aschoff nodules, focal and diffuse inflammatory lesions, focal alterations in cardiac muscle, and valvular verrucae. In animals, alteration of connective tissue was prominent in the endocardium near the valvular attachments, and nodules developed about

the foci of damaged collagen. Perivascular inflammation was frequent but formation of nodules in the adventitia of the arteries was not observed. No actual verrucae with thrombi were noted, although the nodules frequently projected above the surface of the valve to give it a slightly warty appearance.

As Mallory (1947) stated, the parallelism traced between the experimental lesions and the histologic findings in acute rheumatic fever is impressive if not complete. The observations of Rich and Gregory have been confirmed by Fox and Jones (1944) and McKeown (1947) but not by More and McLean (1949). Kyser, McCarter and Stengle (1947) also have produced a similar type of myocarditis in rabbits with horse serum and have made the additional significant observation that antihistaminic drugs, such as diphenhydramine (Benadryl), will impede the development of the lesions.

Cavelti in 1947 found that rats immunized with combinations of killed streptococci and rat heart or connective tissue formed auto-antibodies to these tissues, demonstrable *in vitro*; and that the animals, apparently as a result of the pathogenic action of these antibodies, developed changes affecting chiefly the valves and the other connective tissue structures of the heart which resembled those of rheumatic fever. His hypothesis of the genesis of rheumatic fever is as follows: During or following the streptococcal infection which precedes a rheumatic attack by about 2 to 3 weeks, an autogenous antigen is formed by a reaction in which streptococcal substances or their products combine with components of tissues, perhaps of connective tissue of the host. This antigen incites formation of specific antibodies which in turn precipitate the rheumatic lesions by reacting *in vivo* with the antigen situated in the tissues.

Clawson in 1945 was unable to produce endocarditis in rats by the injection of foreign proteins but was able to produce valvular lesions closely resembling acute rheumatic endocarditis in a high percentage of rats by injecting either green-producing or hemolytic streptococci into the blood stream. Lesions similar to those of bac-

terial endocarditis of human beings were produced on the same valve or on other valves in association with the rheumatic-like vegetations.

In an interesting study, Murphy and Swift (1949, 1950) were able to reproduce in rabbits cardiac lesions, including granulomata resembling Aschoff bodies, by repeated intracutaneous injections, approximately at monthly intervals, of streptococci of different serologic types. Murphy (1952) described "myocardial-fiber Aschoff bodies," by which he meant granulomata developing from injured myofibers. These structures have large basophilic, mononucleated or multinucleated cells and an acellular necrotic center representing the necrotic myocardial fiber. The cellular portion of the structures may represent proliferating nuclei of muscle, usually situated adjacent to the area of necrosis, and reactive, syncytial, multinucleated cell masses, probably of muscular origin. Murphy found these structures in the hearts of 12 patients who died of active rheumatic fever. We have seen these structures, especially in children with acute rheumatic fever, but also in certain instances of hypersensitivity. We do not believe that they are specific lesions characteristic of rheumatic fever. When present in rheumatic fever, they may be caused by a different agent from that causing the true Aschoff body. The original foci of necrosis may be allergic in nature. These structures were apparently also observed by Aschoff (1919) who mentioned that, in addition to the specific rheumatic nodules, he occasionally had encountered parenchymatous granulomata. Robinson (1954) concluded that further studies in rabbits infected with streptococci only, will not result in the experimental production of rheumatic fever.

In our opinion, there is only one structure that is characteristic of acute rheumatic fever and it is so specific that all experimental work must depend upon its reproduction. This is the classic Aschoff body (see page 653). Only the experimental reproduction of an unequivocal Aschoff body will solve the riddle of rheumatic fever. In the light of strict criteria, we do not believe that a true Aschoff body has yet been reproduced experimentally.

It is fairly obvious from a review of the conflicting experimental data that no final conclusion as to the etiology and pathogenesis of rheumatic fever can yet be made. The evidence indicating that the lesions of rheumatic

fever are the result of a hypersensitive reaction (anaphylactic hypersensitivity, Rich and Gregory) is impressive but, as Mallory pointed out, the usual stigmata of allergy are lacking in cases of clinical rheumatic fever and direct proof of anaphylactic sensitization in the human being has yet to be advanced.

Streptococcal Antigens in Serum. From numerous investigations of hemolytic streptococci, based principally on the painstaking studies of Lancefield (1940-41), it is generally agreed that streptococci of group A cause most of the hemolytic streptococcal infections in man. Rantz and associates (1952) reported that among 895 infected children up to 10 years of age, the infection was probably caused by group A streptococci in 140. These streptococcal infections have also been correlated with acute rheumatic fever by many investigators. Rammelkamp and co-workers (1952) remarked that rheumatic fever, whether occurring sporadically or in epidemics, appears to have a relatively constant relationship to the incidence of group A streptococcal infections and that rheumatic fever develops in approximately 3 per cent of all persons infected with group A streptococci. The attack rate following such streptococcal infections appeared to be independent of factors such as geographic areas and clinical manifestations of the streptococcal infection, illness being initiated solely by the streptococcus of serologic group A.

The prevalent opinion that streptococci of group A cause rheumatic fever in man is based not so much on the actual demonstration of these organisms in blood cultures and certainly not on their isolation from the heart valves or the myocardium, but rather on the demonstration in the blood serum of various antigenic components of streptococci of group A. These include streptolysin O, streptokinase, hyaluronidase, hyaluronic acid and other substances, all of which are extracellular products of the streptococcal cell. In pertinent tests, determination is made of the amount of antiserum required to inhibit the biologic activity of a constant and standardized amount of the enzyme or toxin. The specificity of the reac-

tion is determined by the substrate employed, viz., lysis of red cells in case of streptolysin O, lysis of a fibrin clot by plasmin in the case of streptokinase, and hydrolysis of polymerized hyaluronic acid and desoxyribonucleic acid by hyaluronidase and desoxyribonuclease, respectively (McCarty, 1952).

One of the first, and the most widely used, of the antibody tests is the test for antistreptolysin O. It is sometimes maintained (McCarty, 1952) that 80 to 85 per cent of patients with rheumatic fever have a significant increase in concentration of antistreptolysin O and a similar increase in percentage of antistreptokinase. Moreover, 95 per cent of patients supposedly show a rise in either one or the other of these antibodies.

These antibody studies also enable the clinician to recognize rheumatic fever. However, it should be quite clear that these tests are designed for detection of products of the streptococcal cell. While most of the evidence at present seems to favor the streptococcal cause of rheumatic fever, there is still no conclusive evidence that a streptococcus is actually responsible for the disease.

Abnormal proteins have been demonstrated in the blood serum in the acute stage of rheumatic fever. It has been found that, in addition to and distinct from the antibody response, a number of nonspecific changes occur in the blood of patients with acute infectious diseases; unlike true antibodies, their concentration is greatest soon after the onset of the illness, and with clinical recovery, they disappear. Among these "acute-phase reactions" in infectious diseases and also in acute rheumatic fever, are elevation of the rate of sedimentation of erythrocytes and presence of C-reactive protein. C-reactive protein was originally shown to be a precipitate of serum formed in the presence of somatic C-polysaccharide of pneumococci. This protein is said to be regularly present in the serum during active rheumatic fever but may be absent from the serum in conditions which may be confused with rheumatic manifestations (Anderson and McCarty, 1950). However, it may be present in a number of other diseases, such as rheumatoid arthritis, subacute bacterial endocarditis, acute appendicitis, periarteritis nodosa, dermatomyositis, acute glomerulonephritis, and especially chronic glomerulonephritis. Other "acute-phase reactions" in rheumatic fever include serum mucoprotein (Kelley *et al.*, 1950) which is soluble

in perchloric acid and insoluble in phosphotungstic acid. Significant elevations in the mucoprotein level are found in children with bacterial and viral infections, so-called collagen diseases, malignant neoplasms, and rheumatic fever. Also the serum level of a nonspecific heat-labile inhibitor of hyaluronidase is elevated in acute infections, including rheumatic fever, and Good and Glick (1950) demonstrated that this elevation is a good index of activity of disease in rheumatic fever. These reactions may in the future aid in the establishment of the diagnosis of rheumatic fever, but at present they are still nonspecific.

The significance of hyaluronic acid and hyaluronidase in the pathogenesis of rheumatic fever awaits the accumulation of further experimental studies (J.A.M.A., 1949). A possible relationship between hyaluronic acid, hyaluronidase and rheumatic fever is suggested by: (1) the proposal of Klinge that rheumatic diseases are primarily diseases of the cement substance, (2) the fact that sulfonamide compounds, admittedly inactive in rheumatic diseases, have no influence on hyaluronidase (Guerra, 1946); (3) the relatively low quantities (one-sixth to one-half of normal) of plasma enzymes with anti-invasive reactivity in patients with rheumatic fever as compared with healthy persons (Haas, 1946); (4) the inhibitory action of small amounts of sodium salicylate on the spreading of India ink or dye injected together with hyaluronidase (Guerra, 1946; Meyer, 1947); (5) the reports of Quinn (1948) and Harris and Harris (1949) that the mean titer of an antibody to streptococcal hyaluronidase (spreading factor) was significantly higher in sera of patients with rheumatic fever than in sera obtained from convalescents of streptococcal or other infections, or from normal persons; the additional statement by Harris and Harris that the titer of antihyaluronidase in the sera correlated well with the activity of the rheumatic fever process; and (6) the observation in 1944 by Crowley that Types 4 and 22 were the only strains of Group A streptococci which did not contain hyaluronic acid, but did produce hyaluronidase. A report from the Committee on Rheumatic Fever (January, 1950)

includes a statement that there were no reported instances of rheumatic fever following infection with Types 4 or 22, Group A streptococci. Thus it appears likely that rheumatic fever occurs subsequent to an infection with those strains of Group A streptococci which contain hyaluronic acid.

Guerra is of the opinion that rapid extension of the involvement of mesenchymal tissue in rheumatic fever suggests a partial removal of the protective barrier (hyaluronic acid?) offered by the tissue ground-substance. Hyaluronidase is one of the substances capable of overcoming this barrier, although other enzyme systems may also be involved.

Lack of specificity of the relationship between hyaluronidase and rheumatic diseases is suggested by evidence that: (1) the inactivation of hyaluronidase by human serum is a complex reaction, the details of which are not yet completely understood; (2) the presence of inorganic ions such as chloride and phosphate may be as important as the relative concentrations of hyaluronidase and serum in patients with rheumatic disease (Meyer and Ragan, 1948); (3) changes in chondroitin sulfates and their protein complexes may be of greater importance for the rheumatic processes than the changes associated with hyaluronic acid (Meyer and Ragan); (4) Epstein and co-workers (1949) have reported that patients with active rheumatic fever did not have higher anti-hyaluronidase titers than did children with inactive rheumatic fever or those following streptococcal infection, but it was noted that these workers used bovine hyaluronidase as their test substance instead of the streptococcal hyaluronidase employed by Quinn, and by Harris and Harris; and (5) oral administration of salicylates affects the hyaluronic acid in synovial fluid, but it is unlikely that inhibition of hyaluronidase is the only (or even the most significant) *modus operandi* for the known antirheumatic effects of salicylates.

The evidence of a relationship between inactivation of hyaluronidase by human serum and the rheumatic diseases furnishes an interesting theory to explain the action of salicylates in rheumatic fever. However, at the present time the evidence is thought to be tentative rather than conclusive.

MYOCARDITIS

Any discussion of rheumatic heart disease may well begin with the myocardium for three reasons. First of all, as White (1951) so well stated, "The myocardium is the most important part of the heart. If it is sound, a great deal of disease of endocardium and pericardium and great vessels, of valvular deformities and septal defects, and of strain from hypertension can be endured for a surprising number of years; if it is seriously diseased or fails, death may come quickly even though all the rest of the cardiovascular system is perfect." Secondly, the myocardial lesion is the foundation of our knowledge concerning the rheumatic injury. The modern study of the histopathology of rheumatic fever began with Aschoff's description (1905) of the rheumatic nodule and his recognition that the nodule was the characteristic lesion of this disease. If one recognizes and fully understands the rheumatic nodule of the myocardium, he will understand better the various other histologic manifestations of rheumatic fever. Finally, the diagnosis of myocarditis is one of the most difficult for the clinician to make. It has been pointed out (Saphir, 1941) that the frequency of the diagnosis of myocarditis has fallen abruptly. Not so many years ago, most elderly patients who died had "chronic myocarditis" written on their death certificates. Now the term is in large part abandoned. Such wide swings in the medical pendulum indicate the lack of knowledge and the intrinsic diagnostic difficulties of the condition. If any improvement is to be made in this field of medical practice, it may well begin with a sound knowledge of the morphologic basis of the disease.

The gross appearance of the myocardium of patients dying of active rheumatic fever may reveal little that is abnormal. Enlargement of the heart is usually present and produces a globular appearance. On opening the chambers, the enlargement is observed to be the result of hypertrophy and dilatation of the ventricles, particularly of the left ventricle (Figure IX-1). This is true even in those

cases in which there is no mechanical embarrassment, such as valvular deformities or pericardial adhesions, to explain the hypertrophy. The thickening of the ventricular wall is associated with thickening and lengthening of the papillary muscles and the dilatation of the ventricles is associated with dilatation of the atrioventricular rings. The latter may be so extensive as to give rise to slight degrees of insufficiency or incompetence. The gross abnormalities of the heart associated with various valvular deformities will be discussed for each valve separately.

The microscopic appearance of the reaction of the myocardium to rheumatic injury is most pronounced in the connective tissues of the heart, but evidence of direct injury to the myocardial fibers also is sometimes observed. For the sake of clarity, the histologic appearance will be discussed in 4 divisions: (1) focal interstitial myocarditis (the rheumatic nodule); (2) diffuse interstitial myocarditis; (3) direct injury to the muscle fibers; and (4) lesions of the conduction system.

*Focal Interstitial Myocarditis: The
Aschoff Body*

Since Aschoff's classic account (1905) of

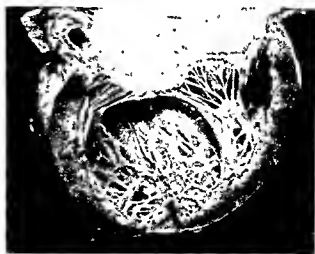


Figure IX-1. Hypertrophy and dilatation of left ventricle in acute rheumatic fever. Patient was a boy 14 years of age. The heart weighed 352 Gm. (estimated normal weight, 216 Gm.). Note verrucae on the mitral valve.



Figure IX-2. Aschoff nodule. Early stage with fibroid degeneration of the collagen.

a. Mallory's phosphotungstic acid-hematoxylin stain X 215.

b. Hematoxylin and eosin. X 600.

the rheumatic nodule, his assertion that the lesion is specific for rheumatic fever has received wide acceptance. It is also now generally recognized that, as in tuberculosis so in rheumatic fever, there is one fundamental lesion with characteristics that may vary with the anatomic site and stage of development but which nevertheless represents the essential reaction of the tissues to the rheumatic injury. Because of this it is perhaps wise to start this discussion of the cardiac lesions in rheumatic fever with a fairly thorough description of the rheumatic nodule.

Although the histologic characteristics of rheumatic cardiac injury have been studied intensively and frequently described since Aschoff's report in 1905, with a few noteworthy exceptions (Geipel, 1905; Thorel,

1910; Pappenheimer and Von Glahn, 1924, 1927; and Talalajew, 1929), attention has been concentrated primarily on the proliferative and exudative phases of the inflammatory reaction to the neglect of what is now widely accepted as the primary injury to the connective tissue. The lack of study of this phase of the inflammatory process is understandable because it is relatively poorly developed in the myocardial lesions and often obscured by the exudative and proliferative processes. We are indebted to Klinge in particular for renewed interest in this phase of the rheumatic inflammatory response. In 1933 he emphasized that the importance of this primary rheumatic injury becomes apparent only by the systematic study of the rheumatic injury as it occurs in other parts of the heart, particularly the pericardium, and in other structures such as the synovial membranes, periarticular connective tissues and skin where the early alterative phase is better developed.

Of great importance also to an understanding of the significance of the rheumatic injury is the concept that the lesions pass through successive stages of development (Klinge 1933, Gross and Ehrlich, 1934) and that the age of any particular lesion can be estimated by its histologic features. It must be recognized, however, that interpretation of the life cycle of these lesions must be qualified by the knowledge that reactions to the rheumatic injury vary with the severity of the infection, with the patient, and with the organ involved. As Clawson (1929) in particular emphasized, the histologic characteristics of lesions within the same organ vary greatly in the extent to which the degenerative, exudative or the proliferative phases have developed. Thus alterative, exudative or proliferative types of reaction may predominate or all three may be present side by side. According to Andrci and Ravenna (1937), the time required for the development of the various stages cannot be accurately predicted by the histologic appearance of the lesion. They pointed out that no one knows how long a granuloma, for example, a tubercle, may persist and they expressed the belief that the presence of the

Aschoff body is neither definite proof of active rheumatic carditis nor evidence that a phase of activity has occurred recently.

Early (Alternative) Stage. According to Klinge (1933), typical Aschoff bodies are not present in the myocardium of patients dying within the first few weeks after onset of rheumatic fever. The first observable phase in the development of the rheumatic nodule is swelling and edema of the connective tissue fibers (Figure IX-2a, b), which stain intensely with eosin and become wax-like and refractile. Fusion may occur at the points where they cross one another. The altered tissue assumes the staining characteristics of fibrin and this leads to the term "fibrinoid swelling" or "fibrinoid degeneration" of the collagen. In the early stages of this process, the individual fibrils of the connective tissue can be shown by silver impregnation to remain intact though separated as if by edema (Figure IX-3). In later stages actual necrosis of the fibrils frequently occurs. In the meshes between the fibers there are fibrin-like masses or precipitated protein. The cellular components of the nodule at this early stage are not increased in number but appear to be shrunken. Lymphocytes and plasma cells are usually present in variable numbers. Variations in the relative numbers and in the arrangement of collagen fibers, cells and precipitated protein give rise to somewhat different histologic types of rheumatic nodules. Gross and Ehrlich (1934) have described small-cell, coronal and reticular types in this early stage.

In some instances the so-called fibrinoid degeneration may be absent but in other cases it may be so severe that it simulates a severe degenerative process which may be indistinguishable from that of acute septic processes. As Clawson (1929) has indicated, occasionally cellular exudation may be prominent in the lesion and abscesses may seem to be present.

The interpretation of the early alternative lesion (fibrinoid degeneration) has aroused some disagreement. Although Klinge and others described it as a true degenerative process of the connective tissue, some (Clark *et al.*, 1936, Graef *et al.*,



Figure IX-3. (Same case as Figure IX-2.) Aschoff nodule. Early stage with fibrinoid degeneration of collagen. Gomori's reticulum stain, X 580.

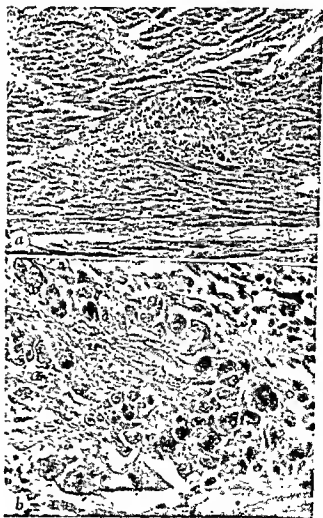


Figure IX-4. Aschoff nodule, granulomatous stage. Giant cells are evident. Hematoxylin and eosin. a. X 110. b. X 420.

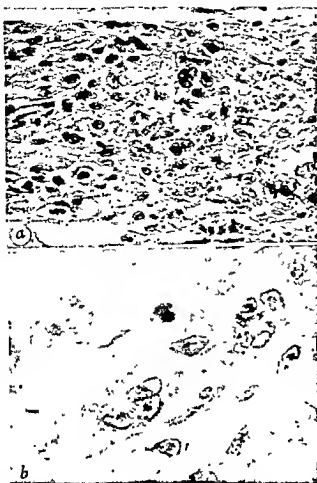


Figure IX-5. Aschoff nodule, granulomatous stage. Hematoxylin and eosin.

- a. Central clumps of fibrin or necrotic collagen X 400.
 b. Giant cells with ragged cytoplasm X 960.

1937) have held that the fibrin-like appearance and reaction of the tissue were merely the result of exudation of plasma and infiltration of the connective tissue with fibrin. Others (Klemperer *et al.*, 1942) have regarded it as a "coagulation" of the ground substance. According to Altschuler and Angevine (1949), the common feature of fibrinoid formation is the precipitation of the acid mucopolysaccharide of the ground substance of the connective tissue. The precipitant in some instances is probably an alkaline protein derived from the necrosis of tissue or the interaction of the tissue with a damaging agent.

Granulomatous Stage. The second phase in the development of the Aschoff body is well advanced one month after the onset of the illness. At this time proliferating and hypertrophied connective tissue cells and sometimes giant cells dominate the picture (Fig-

ure IX-4a, b). The central portion of the nodule usually contains a small amount of swollen, fragmented and occasionally necrotic collagen and sometimes masses of fibrin (Figure IX-5a). The large mononuclear and multinuclear cells usually have vesicular nuclei and a basophilic cytoplasm when stained with hematoxylin and eosin. Characteristically, the cytoplasm has ragged edges and there may be pseudopods or streamers (Figure IX-5b). With Pappenheim's pyronine-methyl-green stain, the cytoplasm stains a brilliant red. The nuclei are often hypertrophied and may appear pyknotic, fibrocytoid or owl-eyed, depending on the arrangement of the chromatin.

The owl-eyed appearance of the nucleus is a characteristic of the Anitschkow myocyte (1913). This particular cell also has been called "myocardial reticulocyte" (Ehrlich and Lapan, 1939) and "cardiac histiocyte" (Downey, 1941). It is normally found in the heart and its valves. On longitudinal section the nucleus of this cell is elliptic and vacuolated, except for a serrated bar of chromatin in the center. Fine fibrillar structures extend at right angles from the central bar toward and in many cases to the nuclear membrane (Figure IX-6a). In cross-section the nucleus is round or nearly so and has a dark mass of chromatin in the center from which chromatin fibrillae extend, giving it an owl-eyed appearance. In normal hearts little cytoplasm is observed but when inflammation is present, cytoplasm appears in increasing amounts and stains more deeply with hematoxylin. The Anitschkow myocyte is often the chief constituent of the reaction of the heart to injury and is particularly prominent in the rheumatic nodule (Clawson, 1941). It constitutes the most characteristic feature of the lesion and is sometimes called "Aschoff" cell (Boyd, 1944).

The giant cells in the lesion are smaller than those of tuberculous lesions or in foreign body granulomas. Their cytoplasm is less abundant and is slightly basophilic. Their nuclei are relatively large and lobular and exhibit marked polymorphism. These giant cells are few in number, are located centrally and are in close relation to one another (Fig-

ures IX-5b and IX-6b). In these features they resemble more closely the giant cells of Hodgkin's disease than those of tuberculosis. Lymphocytes and plasma cells are to be seen in varying numbers, together with an occasional polymorphonuclear leukocyte. Characteristic also are the arrangement of the various cells and the perivascular location of the Aschoff body. The cells are arranged in parallel rows, sometimes concentrically about the blood vessel.

This granulomatous phase of the rheumatic nodule is the one that is usually described in textbooks as typical of the Aschoff body. As Gross and Ehrlich (1934) emphasized, it is only when the nodule has reached this stage of development that certain diagnosis is possible, and that the lesion is specific, differing from lesions found in the myocardium in non-specific inflammations. We believe that only in this stage is the Aschoff body characteristic and pathognomonic of rheumatic fever. This is the lesion that must be experimentally reproduced in order to clarify the problem of rheumatic fever.

Healing Stage (3 to 6 Months). This third phase in the life cycle of the Aschoff body is dominated by regressive phenomena. The cytoplasm of the characteristic cells, although still basophilic, is diminished in amount, the outlines of the cells are sharp and the cells become spindle-shaped. Giant cells become scarce and the nuclei become fibrocytoid (Figure IX-7a, b). The spindle-shaped cells become transformed into fibroblasts with delicate collagenous fibrils. The entire collection of cells begins to assume a definite direction within the planes of the myocardial bundles. The delicate collagenous fibrils fuse into dense collagenous bundles and the final stage is the development of the scar which characteristically lies between the muscle bundles. Peculiar onion-shaped scars which broaden the perivascular connective tissue and on whose edge some muscle fibers are destroyed were described by Klinge (1933) as rheumatic in origin. Occasionally they are visible grossly but usually they are microscopic in size. In 65 of 139 hearts from patients who previously had definite rheumatic fever ur

were suspected of having it, these perivascular scars were present (Wild, 1933). Their absence, of course, does not exclude a previous rheumatic inflammation. According to Rössle (1935) and Morpurgo (1936), healing with the formation of a scar may follow the early alternative phase of inflammation without the development of the granulomatous stage.

Location. The rheumatic nodule is usually found near or in association with blood vessels or close to the endocardium. In general, it is found in relation to the adventitia of medium-sized or small arteries. In the myocardium they are found most frequently in the interventricular septum and on the posterior wall of the left ventricle. The other most common sites, in order of frequency, were: left posterior papillary muscle, pulmonary conus, posterior wall of the left atrium



Figure IX-6. Aschoff nodule, granulomatous stage. Hematoxylin and eosin.

a. Anitschkow myocytes or myocardial reticulum. X 1360.

b. Syncytial coronal type. X 435.

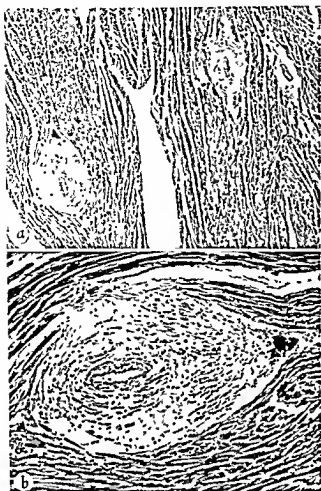


Figure IX-7. Aschoff nodules, healing stage. Similarity of cells to fibroblasts should be noted. Hematoxylin and eosin. *a*, X 30. *b*, X 85.

and the myocardial wedge between the aorta and left atrium. Clawson (1941) found them as frequently in the apex as in any other part of the heart.

Size and Shape. According to Geipel (1905), the rheumatic nodule can reach a length of 880 micra and a width of 80 micra. Clawson (1941) stated that marked variations were noted in the size of the nodules. They sometimes consisted of only a few cells near or surrounding blood vessels and sometimes they were large enough to extend entirely across a section more than a centimeter in width. The nodule, as described by Aschoff (1905), was rosette- or fan-shaped. It tended to become elongated and irregular and to extend between the muscle fibers. According to Geipel, the nodules were round, oval or fusiform. Cross and Ehrlich (1934) described them as being occasionally spherical but gen-

erally oval, dish-like or spindle-shaped. Klinge (1933) stated that the nodule is usually spindle-shaped but often appears stretched longitudinally. Sometimes it is plump and short. The shape varies with the anatomic relationship and the amount and the extent of the space available. Thus, between individual muscle fibers one finds small nodules, whereas large ones are present in the larger connective tissue spaces.

Frequency. Figures on the incidence of Aschoff bodies in hearts which are the sites of rheumatic inflammation vary from 32 per cent (Libman, 1923) to 95 per cent (Whitman and Eastlake, 1920). Clawson (1929), in a review of the incidence reported by various investigators, found that the mean incidence in 190 cases from various sources was 69 per cent.

Specificity. Since Aschoff's conclusion that the inflammatory nodules described by him were specific for rheumatic fever, most investigators have supported his views.

Workers who have held this opinion were Geipel (1905), Coombs (1909, 1924), Fraenkel (1912), Bracht and Wachter (1909), Huzella (1914), Thalheimer and Rothschild (1914), and Fahr (1921, 1930). More recently Cross and Ehrlich (1934) and Saphir (1941, 1942) have re-emphasized this view.

In support of this opinion it has been stated that: (1) The nodules have distinctive histologic characteristics; (2) they are frequently encountered in acute rheumatic fever while the characteristic Aschoff bodies are never found in other acute infectious diseases; and (3) nodules of similar morphologic and staining characteristics have not been produced experimentally.

Clawson (1941), however, has contended that the type of inflammation found in the rheumatic nodule in man cannot be said to be characteristic because of the following reasons: (1) In a relatively high percentage of cases of acute rheumatic endocarditis the Aschoff nodules are not found in the myocardium; (2) they are not infrequently found in the heart in cases of nonrheumatic infectious disease; and (3) nodular areas with a similar morphologic cellular appearance have

frequently been produced experimentally in rabbits by the injection of streptococci.

With respect to the first reason, the frequency of finding of true Aschoff bodies in fatal cases of acute rheumatic fever probably depends upon the number of blocks examined from the myocardium. In a study of subacute bacterial endocarditis superimposed on rheumatic endocarditis in children, in which numerous sections were taken from the myocardium, we were able to find Aschoff bodies in every one of the hearts, in a diligent search in a number of other conditions, we have never found any characteristic Aschoff bodies. Concerning structures resembling Aschoff bodies in scarlet fever, and bodies described by Bracht and Wachter (1909), see page 744. On the other hand, however, we have seen Aschoff bodies in the myocardium of children who died of diphtheria or other infectious disease, but investigation of the past history always disclosed that the patient's final illness was preceded or complicated by acute rheumatic fever.

As stated above, we are not convinced that typical Aschoff bodies have ever been produced experimentally. A scrutiny of relevant photomicrographs and their comparison with the typical body in the granulomatous stage should be revealing to the unbiased observer. Lesions resembling the bodies and so-called healing Aschoff bodies must not be accepted as evidence. We fully realize that, if we are to adhere to such rigid criteria for identification, we may fail to recognize certain Aschoff bodies, and thus fail to make a diagnosis of rheumatic myocarditis. On the other hand, we will be less likely to err if cellular infiltrations resembling Aschoff bodies, regardless of their location in the heart, are not accepted as true Aschoff bodies. These strict criteria are of particular importance today in the evaluation of experimental work claiming to reproduce rheumatic fever, since certain hyperergic reactions in the myocardium closely resemble Aschoff bodies. For a discussion of so-called "myofiber" Aschoff bodies, see page 650.

It is obvious that the specificity of the Aschoff body is a highly controversial subject. Conclusions from the mass of conflicting data and opinions are difficult. It is our opinion that the typical Aschoff body in its fully developed granulomatous stage is as specific for rheumatic fever as the tubercle is for tuberculosis. Pathologists, however, are not satisfied with knowing the histologic reaction

of the infectious agent but demand in addition that the causative agent be demonstrated by either histologic or cultural methods or by animal inoculation. Since this is not possible in the case of rheumatic fever, the demonstration of the typical rheumatic nodule in its granulomatous stage of development is the best evidence available on which the pathologist may base the diagnosis of rheumatic fever (Mallory and Keefer, 1941). For this reason, utmost caution is recommended before accepting structures as Aschoff bodies.

Golden and Hurst (1953) described alterations in the lesions of acute rheumatic myocarditis during cortisone therapy. The most striking finding was atypical myocarditis characterized by extensive fibrinoid degeneration of the collagen



Figure IX-8. Diffuse myocardial inflammation in rheumatic heart disease. Hematoxylin and eosin.

a. Diffuse infiltration with polymorphonuclear cells. X 160.

b. Diffuse inflammation with presence of large basophilic cells. X 105.



Figure IX-9 Aschoff nodule with destruction of adjacent muscle fibers. Hematoxylin and eosin X 160

but with no or little cellular reaction. They felt that their findings do not indicate that cortisone to any degree prevents the injury to connective tissue that is associated with rheumatic fever and concluded that, despite hormonal therapy, the lesion of acute rheumatic fever runs its natural course.

Diffuse Interstitial Myocarditis

Although diffuse rheumatic inflammation has received little attention compared to that given the rheumatic nodule, it may be of greater clinical importance. Clawson (1940a) stated that it is present in about 18 per cent of cases of acute rheumatic myocarditis. There are great variations in the extent and appearance of this inflammation. The lesions usually consist of edema of the connective tissue with such cellular elements as lymphocytes, plasma cells and macrophages. Occasionally many polymorphonuclear cells (Figure IX-8a) may be seen and on rare occasions a predominance of eosinophils is noted (Watjen, 1921). The diffuse myocardial lesions are most prominent at the base of the valve leaflets.

Romberg (1894) and Takayasu (1909) have described large epithelioid cells in the diffuse inflammation which have an identical appearance with the cells of the rheumatic nodule (Figure IX-8b). Skworzoff (1938) has indicated that diffuse exudative inflammation either may be found about the specific rheumatic granuloma (a perifocal inflammation) or it may appear in-

dependently as a hyperergic reaction analogous to the exudative inflammation of joints and pericardium. He was particularly impressed by the fact that patients who had extensive exudative lesions were principally children and presented an extraordinarily severe course with a clinical picture of myocarditis and a rapidly fatal outcome.

Saphir and Langendorf (1953) described interstitial nonspecific myocarditis in the heart of every one of their patients who died of acute rheumatic fever. They suggested that the electrocardiographic changes in acute rheumatic fever are caused by nonspecific myocarditis rather than by the presence of Aschoff bodies in the interstitial tissue. The nonspecific changes include necrosis of muscle, interstitial myocarditis and serous myocarditis.

Direct Myocardial Damage

The discrepancy so frequently observed between the degree of functional impairment and the minor morphologic signs of inflammation demonstrable by the pathologists has led many to postulate and search for evidence of direct injury to the myocardial fibers. The inadequacy of histologic methods to demonstrate such changes, so deplored by Coombs (1907, 1909, 1924), many years ago, still remains.

Direct injury to the heart muscle is observed in the vicinity of the rheumatic nodules and has been interpreted to be the result of pressure atrophy of the muscle fibers (Figure IX-9). Rich and Gregory in 1943 stated that necrosis of small foci of cardiac muscle occurs but that it is slight or absent in many of the less severe instances of rheumatic carditis. Such slight and nonspecific changes as cloudy swelling and waxy degeneration of the muscle fibers have been described. Coombs in 1924 stated that infiltration of the muscle cells with fat was the most definite phenomenon seen but it is not found in every case and it also is a feature of the later stages of the disease when active inflammation has subsided. Rarely, infarction of the myocardium is observed (Klinge, 1933) as a result of occlusion of a small vessel damaged by the rheumatic lesion. This may well be the explanation for a case of cardiac aneurysm reported by Parkinson and his associates in

1938 and attributed by Turnbull to rheumatic necrosis of the myocardium. (See page 650 for reference to "myocardial-fiber Aschoff bodies" described by Murphy, 1952.)

Lesions of the Conduction System

Impairment of the atrioventricular conduction is common during the course of acute rheumatic fever. The incidence of defects in conduction in this disease varies with different authors, ranging from approximately 27 to 87 per cent (Bruenn, 1937). Reports of histologic studies of the bundle of His describe lymphocytic infiltrations in the region of the node and trunks, fibrous degeneration of the bundle of His with calcification and swelling of collagen. In active rheumatic fever, Gross and Fried (1936) were able to demonstrate a variety of inflammatory and vascular phenomena in the conduction system by a few representative sections in 66 per cent of cases. It is probable that a study of

more sections would have indicated a higher incidence.

Few of these lesions were of a specific or highly characteristic nature. Aschoff bodies were found in the bundle of His in only 2 of the 60 cases of active rheumatic fever. Edema of the bundle was observed in only 15 per cent of cases. More frequently there were accumulations of lymphocytes and occasionally polymorphonuclear cells, plasma cells, macrophages and young fibroblasts. Vascular lesions, such as intimal thickening and hypertrophy of the media, were observed frequently and thrombosis rarely. In cases of inactive rheumatic fever, few lesions were found in the bundle.

In view of the frequent occurrence of lesions of the conduction system, it would seem unnecessary to ascribe impairment of atrioventricular conduction to either the direct effect of toxins on the conduction system or to an increase in vagal tone, as suggested by Bruenn.

ENDOCARDITIS

Valvular Inflammation

General Considerations. The term "endocarditis" has been used almost universally to denote the valvular lesion of rheumatic fever.

Although thus honored by custom and usage, even a cursory histologic examination of an affected valve reveals the inadequacy of the term. The basic lesion is not an endocarditis

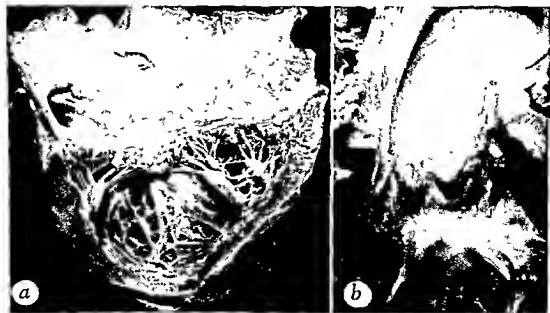


Figure IX-10. *a.* Acute rheumatic mitral endocarditis. Verrucae on line of closure and involvement of left atrium. *b.* Acute rheumatic aortic endocarditis.

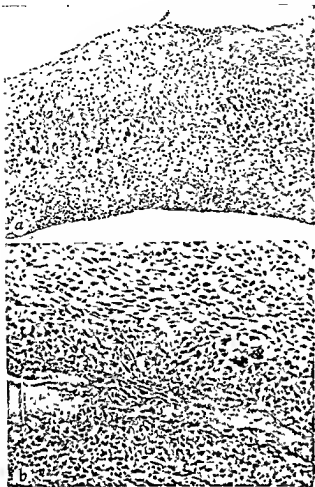


Figure IX-11. Acute rheumatic valvulitis. Hematoxylin and eosin.

a. Mitral valve. Focus of fibrinoid degeneration may be noted on proximal (atrial) surface and granulomatous nodules in the substance of the leaflet. There is a suppurative reaction on the distal (ventricular) surface. X 95.

b. Mitral valve. Bandlike zone of fibrinoid necrosis with giant cells. X 175.

but an inflammatory process of the valve proper—a valvulitis with secondary involvement of the endocardial surface. In the descriptions of valvular lesions in this chapter, the terminology used will be that outlined by Gross and Kugel in 1931 in their study of the topographic anatomy and histology of the valves of the human heart. In this chapter the term *cusps* will be used to designate the component parts of a semilunar valve and *leaflets*, the component parts of an atrioventricular valve or of an unspecified valve.

Gross evidence of rheumatic inflammation is commonly observed in the mitral and aortic valves, less frequently in the tricuspid, and rarely in the pulmonary.

Clawson (1945) reported that "of the 780 cases of rheumatic heart disease in which the valves were affected, there was involvement of the aortic or mitral or both valves in 779 (99.8 per cent)." In 44 (5.6 per cent) the valves on the right side of the heart were affected and in all of these, except one case in which a pulmonic valve only was affected, aortic or mitral involvement was associated (Clawson, 1940a). Histologic examination, however, discloses evidence of inflammation in the tricuspid valve as frequently as in the mitral and aortic (Gross and Friedberg, 1936).

Age and Sex. Disease of the mitral valve commonly occurs in youths and in persons of middle age and is more common in females than males in a ratio of three to two. Rheumatic disease of the aortic valve extends from early childhood to extreme old age. It is commonest in middle and old age; the ratio of occurrence among males compared to females is 3 to 1.

Acute and Subacute Valvulitis. Incidence. Clawson (1940a) studied 796 cases of rheumatic heart disease at necropsy and classified 98 as cases of acute rheumatic endocarditis (Table IX-1).

Gross appearance. The most conspicuous lesions in the early phases of valvular inflammation are the tiny translucent nodules (*verrucae*) which form along the lines of closure or contact (Figure IX-10a, b). They vary in size from less than 1 mm. to 3 mm. and are located on the atrial surface of the mitral and tricuspid valves and on the ventricular surface of the semilunar valves. Occasionally they are distributed elsewhere over the cusps. In later stages of the disease the nodules become more opaque and warty and are red-gray or tawny. They are firm and are not easily dislodged. They may be arranged simply in a row or in clusters of two or three. Occasionally they are fused for a considerable distance and form a pyramidal ridge along the line of closure. They may be observed also on the chordae tendineae and rarely on the papillary muscle. Not infrequently they extend over the posterior leaflet of the mitral valve and onto the endocardium of the left atrium. The nodules tend to form conglomerate mounds on the *corpora arantii*

of the aortic valve and from there extend in rows along the semilunar cusps.

Diffuse thickening of the valves, with the exception of the pulmonic, is a less conspicuous but frequent gross alteration. The scalloped, concave margins of the atrioventricular valves are usually thickened and straight. Occasionally there is an irregular roughening and rarely slight vascularization of the atrial surface of the atrioventricular valves. The normally sharp margin of the cusps of the aortic valve frequently becomes slightly thickened and rounded.

Histologic appearance. The inflammatory process may be present in any portion of the leaflet but is observed most frequently in the proximal layers of the valve (auricularis layer of the atrioventricular valve and ventricular layer of the semilunar valves) with involvement of the spongiosa. Two varieties of inflammatory response may be observed which for descriptive purposes can be distinguished as nonspecific and specific (rheumatic) inflammation.

The nonspecific inflammatory process may involve the entire leaflet or cusp as well as the ring, and consists of edema, increased numbers of capillaries and a variety of inflammatory cells. These cells are chiefly lymphocytes but occasionally polymorphonuclear cells predominate. Rarely are these cells so numerous as to suggest phlegmon (Klinge, 1933). Plasma cells, fibroblasts, macrophages and other mononuclear cells are often present in variable numbers.

If the inflammatory process presents only these features, it does not differ from valvulitis of other causes. In most cases, however, there is also, as Bulloch in 1908 and Coombs in 1909 pointed out, proliferation of peculiar large cells which resemble young fibroblasts (the Aschoff cells already described). These may be arranged in nodules or in rows and generally surround foci of intensely eosinophilic fragmented collagen (Figure IX-11). This is the so-called fibrinoid swelling and degeneration of collagen described by Neumann (1896) and emphasized in recent years by Klinge. According to the latter, the fibrinoid swelling of the connective tissue is the pri-

mary injury to the valve and this may go on to degeneration and necrosis. The proliferative stage follows and consists largely of collections of the large Aschoff cells. They may occur singly or after fusion, as multinucleated giant cells. In many cases the fibrinoid degeneration of the collagen occurs as a bandlike lesion, including a considerable portion of the leaflet (Figure IX-11b). Not infrequently the band of fibrinoid degeneration is found directly beneath the endothelium of the proximal surface (Figure IX-12). In these instances the proliferating cells may be found perpendicular to the altered collagen in a palisaded arrangement.

Gross and Friedberg in 1936 emphasized the occurrence of lesions in the valve rings in acute and subacute rheumatic fever. The inflammatory process is similar to that in the leaflet and Aschoff bodies are present in the valve rings in approximately 10 per cent of cases in which the patient died during the first attack of rheumatic fever. The almost invariable presence and severity of lesions of the valve rings in the active stages of rheumatic fever, together with the fact that these rings may be the only part of the valve affected, suggested to Gross and Friedberg that this is probably the first portion of the valve leaflet involved by the rheumatic process. In the great majority of their cases all the valves were involved, and involvement of only one or two valves was the exception.



Figure IX-12. Acute rheumatic pulmonary valvulitis. Granulonatous nodule in substance of cusp. Hematoxylin and eosin. X 200.

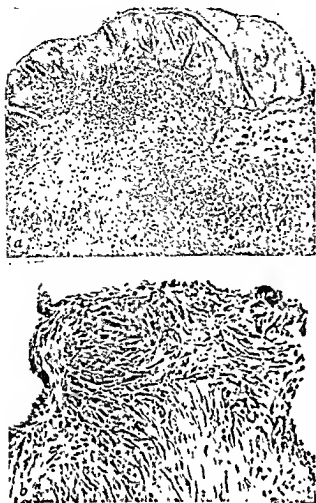


Figure IX-13. Verrucae in acute rheumatic valvulitis. Hematoxylin and eosin.

a. Granulomatous inflammation of substance of leaflet with a platelet of fibrin thrombus superimposed. X 90

b. Extruded portion of valvular collagen which has undergone fibrinoid degeneration. X 150.

Histologic appearance of verrucae. These may have the appearance of platelet and fibrin thrombi deposited on the surface of the valve and stain intensely with eosin (Figure IX-13a) or they may appear as an extruded portion of collagen which has undergone fibrinoid degeneration (Figure IX-13b). In either case there is a marked proliferation of fibroblasts in the region immediately adjacent to the vegetation, as well as edema and numerous lymphocytes.

Pathogenesis of verrucae. For a long time the viewpoint had been held that the pathologic changes in the valves consisted essentially of a piling up of thrombotic masses which came from the blood. Neumann in

1896, Bulloch in 1908, Coombs in 1909 and Swift in 1924 emphasized the appearance of the earliest changes in the subendothelial layers. Coombs stressed the predominance of the proliferative reaction in the valves and pointed out that the deeper structures reacted before there was evidence of injury to the endothelial surface. These observations led to the concept that damage to the deeper structures of the valve occurred first and the formation of vegetations followed later. Although this concept is now generally held (Clawson and Bell, 1926; Holsti, 1927; Darre and Albot, 1929; Shaw, 1929; Jaffé, 1938), the mode of production of verrucae is still disputed. Some workers believe that verrucae represent accumulations of platelets and fibrin (Leary, 1932; Hadfield and Garrod, 1947; Hall, 1948). Others think that verrucae are the result of disintegration and fusion of proliferating cells on the superficial layers of the valve leaflets together with swelling and eosinophilic changes (Gross and Friedberg, 1936). According to Neumann (1896) and others, verrucae are extrusions of foci of fibrinoid degeneration and necrosis, while still others believe that they represent a combination of fibrinoid degeneration with deposits from the blood stream (Koniger, 1903). This latter view is in accord with most of our observations although in some instances we have confirmed Neumann's observations (Figure IX-13b). The location and arrangement of the vegetations give clues as to their pathogenesis. The fact that their commonest site is the mitral valve and that they appear along its line of closure indicates their mode of formation.

As Hadfield and Garrod (1947) have emphasized, the mitral valve closes against the highest pressure exerted anywhere in the circulatory system, and the impact of its surfaces and the mutual compression of those surfaces during systole constitute a degree of mechanical trauma which, although sustained without injury by a healthy endocardium, is sufficient to cause a breach of the surface when an inflammatory focus (the rheumatic nodule) lies immediately beneath it. The superficial destruction of endothelium occurs along the line of closure, and along this line also extrusion of collagen occurs

and platelet thrombi may be deposited. The importance of high pressure and greater mechanical trauma are illustrated, according to Hadfield and Garrod, by the behavior of the valves on the right side of the heart.

Vegetations are found on the tricuspid valve in only about 40 per cent of all cases, if this were simply the result of lower pressure on the right side of the heart, it would be expected that in conditions producing a rise of pressure on that side, tricuspid vegetations would be common. This is actually the case. If the disease recurs after mitral incompetence has been established, vegetations on the tricuspid and pulmonary valves are frequently found at necropsy.

Recurrent Valvulitis. *Incidence.* In the group of 796 cases of rheumatic fever studied at necropsy by Clawson (1940a), 76 cases (9.5 per cent) gave evidence of recurrent rheumatic valvulitis (Table IX-1).

TABLE IX-1

Types of Rheumatic Heart Disease Encountered
in 796 Cases at Necropsy (From
Clawson, 1940)

	Cases	Per Cent
Acute rheumatic endocarditis	98	12.3
Recurrent rheumatic endocarditis	76	9.5
Valve deformities	586	73.6
Incompletely healed	113	19.3
Completely healed	239*	40.8
Calcified, nodular, aortic	234	39.3
Adherent pericardium	36	4.5

* See second footnote to Table IX-2.

Gross appearance. As a result of repeated attacks of rheumatic fever, gross alteration in the valves becomes more pronounced. Thickening, irregularity of the surface and gross vascularization are usually present and are most prominent in the mitral valve. With repeated attacks the thickening tends to become more severe in the distal third of the valve cusps. In the mitral valve the thickened tip may be prolonged over the insertions of the chordae tendineae (Figure IX-14a). The chordae tendineae become thicker and shorter and the papillary muscles are much closer to the margins of the cusps. The thickening of the chordae tendineae is particularly prominent at their insertions into the leaflet where they appear to be absorbed into the latter.

Verrucae in various stages of activity and healing may be observed. Sometimes they can be seen to be superimposed on a ridge of older verrucae at the line of closure, and in other instances a parallel row of fresh verrucae can be discerned (Figure IX-14b, c).

The aortic cusps, in addition to thickening, may reveal considerable shortening as a result of rolling and inversion of the free margins of the cusp toward the sinus pocket (Figure IX-15a). The cusps may also present adhesions at the commissures and verrucae in

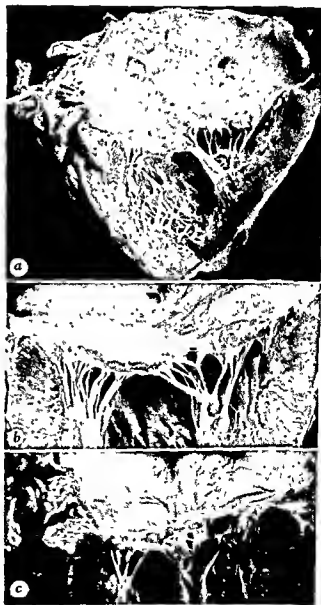


Figure IX-14. Recurrent mitral valvulitis.

- Thickening of valve leaflet with prolongation over chordae tendineae.
- Parallel rows of old and recent verrucae.
- Recent verrucae on a previously damaged leaflet.

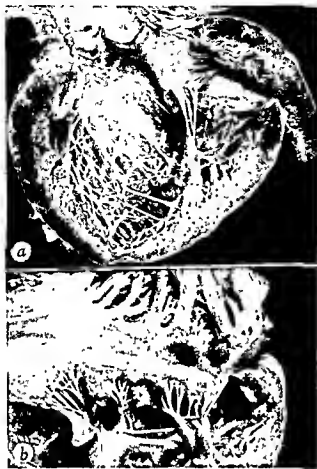


Figure IX-15. Recurrent valvulitis.

a. Aortic valve. Recent verrucae may be noted on a previously damaged cusp.
b. Tricuspid valve.

various stages of activity. The latter may extend from one cusp to another across the commissures. Abnormalities in the valve pockets include verrucous ridges and folds. An interesting feature of recurrent valvulitis is the higher incidence of verrucae on the valves of the right side of the heart (Figure IX-15b). This may be related to the increased pressure in the pulmonary circulation following deformity and dysfunction of the mitral valve.

Histologic appearance. Whereas the thickening of the valves in acute and subacute valvulitis is the result only of edema and inflammation, in recurrent valvulitis there is evidence of considerable fibrosis and elastic tissue proliferation in addition to inflammatory changes in various stages of activity. The inflammatory cells are predominantly lymphocytes with smaller numbers of polymorphonuclear cells, plasma cells and macrophages.

The fibrosis and inflammation involve the rings as well as the leaflets, and the fibrous and elastic thickening is particularly prominent at the subvalvular angles. The intervalvular fibrous tissue is almost always involved also. In striking contrast to the appearance of acute valvulitis is the presence of numerous arteries with thick muscular walls in the ring and leaflet. In cases of longer duration, the walls of these vessels become fibrotic. The increased vascularity is one of the most conspicuous features of recurrent valvulitis (Figure IX-16a). Another distinct difference from the appearance of the leaflet in acute valvulitis is the marked fibrosis and thickening of its tips. There are usually more verrucae in recurrent valvulitis and many of them show evidence of organization. In the valve pockets the endocardium is usually thickened, and sometimes inflammatory polypoid vascular

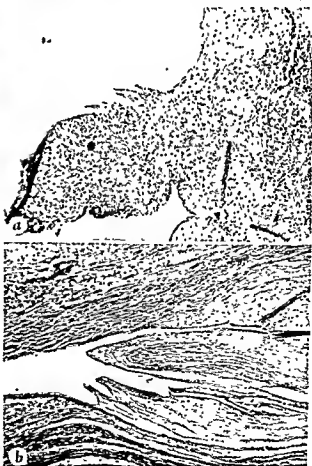


Figure IX-16. Recurrent rheumatic valvulitis. Hematoxylin and eosin.

a. Tip of mitral valve. X 50.

b. Polypoid projections in subvalvular angle, X 60.

TABLE IX-2

Combinations of Valve Involvement in 779 Subjects with Rheumatic Heart Disease
(From Clawson, 1940)

	A*	M	T	P	AM	AT	AP	AMT	AMP	AMTP	MT	MTP	TP	Total
Acute rheumatic	2	43	0	1	24	0	0	10	0	9	9	0	0	98
Recurrent rheumatic	2	21	0	0	30	1	0	11	1	4	6	0	0	76
Valve deformities.														
Incompletely healed	4	65	0	0	28	0	0	8	0	1	7	0	0	113
Completely healed	17	149	0	1	45	0	0	17	0	0	9	0	0	238†
Calcified, nodular, aortic	136	0	0	0	92	1	0	5	0	0	0	0	0	234
Adherent pericardium	6	11	0	0	2	0	0	1	0	0	0	0	0	20
Totals	167	289	0	2	221	2	0	52	1	14	31	0	0	779

* A, M, T and P represent first letters of valves affected.

† Clawson reported data on only 238, not on 239 cases indicated in Table IX-1.

projections of the endocardium (Figure IX-16b) are present (Gross and Friedberg, 1936). In addition to these various nonspecific signs of inflammation, Aschoff bodies frequently are found in the fibrosa or spongiosa layers of the leaflets.

Chronic Valvulitis. This condition is encountered at autopsy after one subsiding or several recurrent bouts of rheumatic fever without recent exacerbation. In other words the end results, usually of repeated attacks, of rheumatic inflammation may be noted and the last attack before death may be subsiding but the lesion has not yet completely healed. This concept is in accord with the idea that rheumatic fever is a disease of recurrent acute attacks rather than a sustained chronic inflammatory process.

Incidence. In 113 of 796 cases of rheumatic heart disease Clawson (1940a) found valvular deformities which were incompletely healed (Table IX-1). In 4 of these 113 cases the aortic valve was involved alone, in 65 the mitral alone, in 28 the aortic and mitral valves were involved, in 8 the aortic, mitral and tricuspid, in 1 the aortic, mitral, tricuspid and pulmonic and in 7 the mitral and tricuspid (Table IX-2).

Gross appearance. The changes already described in recurrent valvulitis are present and are more advanced in cases of chronic valvulitis (Figure IX-17a, b). Usually the thickening and fibrosis have resulted in a loss of elasticity and narrowing of the orifice. Occasionally retraction and curling have led to

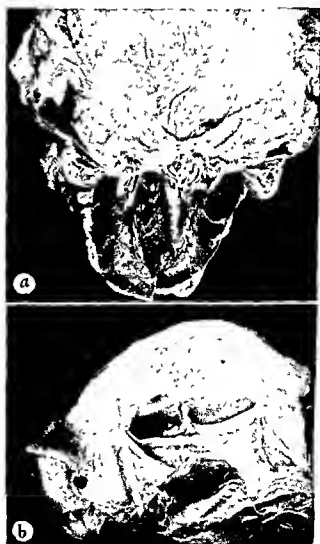


Figure IX-17. Chronic valvulitis.

a. Mitral valve with severe stenosis of orifice. Note greatly enlarged left atrium. Thickening and deformity of leaflets and thickening and shortening of chordae tendineae.

b. Aortic valve. Fusion of cusps and rolling of the free margins are noticeable.

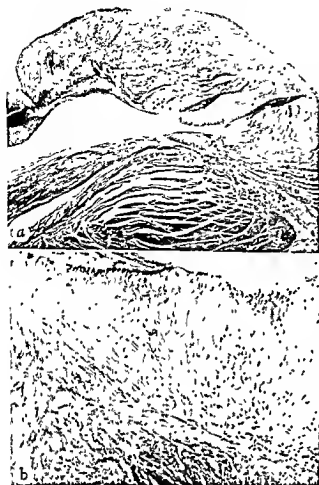


Figure IX-18. Chronic mitral valvulitis. Hematoxylin and eosin

a. Note fibrosis and paucity of inflammatory cells. X 8. b. X 85.

more insufficiency than stenosis (Clawson, Bell and Hartzell, 1926). Thickening, fusion, absorption and shortening of the chordae tendineae are severe, and not infrequently the papillary muscles are almost in contact with the margins of the valve. The normally sharp pocket angles of the atrioventricular valves are broadened. Occasionally fibrous adhesions extend from the leaflet to the ventricular wall and obliterate the angle. The regions of the valve rings and the subvalvular angles are thickened and prominent.

In addition to severe diffuse thickening of the leaflets, there is evidence of deposition of calcium salts. These deposits may further distort the leaflets and may project through to the atrial and ventricular surfaces. In the aortic valve the calcium is found in the region of the noduli and in the commissures as well

as in the cusps themselves. As a result there is much more distortion than in acute or recurrent inflammation and the cusps are rigid.

The rheumatic verrucae are less frequent than in recurrent valvulitis and are broad and flat. Occasionally nonspecific vegetations are found on valves which are the seat of chronic inflammation, as well as in completely healed deformed valves. These vegetations consist essentially of noninfected thrombi and are not related to active rheumatic inflammation. They are usually flat and they form on the line of closure or on calcified or ulcerated areas unrelated to the line of closure.

Histologic appearance. Signs of active inflammation are less pronounced than in recurrent valvulitis. The thickening which is apparent grossly can be seen to be the result of increased fibrous and elastic tissue throughout the entire leaflet, including the rings and the tips of the leaflets. Lymphocytes and other inflammatory cells tend to disappear and the fibrous connective tissue has become more homogeneous and hyaline (Figure IX-18a).

In the valve rings the annulus frequently is hyalinized. The posterior mitral leaflet frequently reveals the greatest thickening but active inflammation is more likely to be noted in the tricuspid leaflets. All valves are vascularized by capillaries and thickwalled vessels which are more numerous on the superficial layers (Figures IX-18b and IX-19). Calcification is common in the leaflets and the lime salts may be distributed diffusely or in the form of large nodular masses. In the ring the annulus may reveal calcification and formation of bone.

The verrucae are organized by fibroblasts and there are many new collagenous fibers. As healing progresses, the fibroblasts decrease in size and finally disappear altogether. The central part of the verrucae becomes a scar-like structure. The thrombotic vegetations which form on the line of closure of the valves and on calcified and ulcerated portions of the deformed valves have a hyaline appearance and seem to be formed largely of platelets. There is little or no cellular reaction at the base. They rest on the scar-like hyaline connective tissue of the leaflet, and the throm-

bus shows little or no tendency toward organization.

Healed Valvulitis (Valvular Deformities)

In this section deformities which result from rheumatic inflammation will be considered. It should be emphasized, however, that not all valvular deformities are rheumatic in origin. When a valvular deformity is encountered either in the clinic or at necropsy the clinical or morphologic data may not give sufficient evidence to permit the etiologic factors involved to be determined satisfactorily. At present the tendency is to regard all such lesions, particularly when the mitral valve is affected, as rheumatic in origin. The wisdom of such dogmatism may well be questioned. It does not seem that enough is known concerning the valvular damage in a wide variety of toxic, infectious and metabolic processes to dismiss all etiologic possibilities except rheumatic fever in the interpretation of any valvular deformity.

In this connection such studies as those of Baldassari (1909), Czirer (1913) and de Vecchi (1931) should be mentioned. These investigators found histologic evidence of acute valvulitis in children in the presence of such diverse diseases as scarlet fever, diphtheria, bronchopneumonia, meningitis and tuberculosis without gross evidence of valvular damage. From these studies it seems possible that patients, especially children, who survive such infectious processes (Siegmund, 1931) also have acute valvulitis which in some instances may heal and result in valvular deformities. The same may be postulated for the healed stage of bacterial endocarditis (Saphir, 1941, 1942; Moore, 1946). The scarred end-stage of any inflammatory process rarely gives pathognomonic signs of the original etiologic agent.

In a number of cases of clear-cut rheumatic disease, certain morphologic changes are found in the heart which have been covered by the term "rheumatic stigmata." These involve changes in the pericardium, the left atrium, and the valves, principally the mitral valve. Circumscribed obliteration of the pericardial sac, thickenings of the mural endocardium of the atrium, and rugal elevations situated just above the posterior leaflet of the mitral valve on the posterior wall of the left atrium are often regarded as characteristic.

Microscopically, the arrangement of mononuclear cells in a palisaded fashion, perpendicular to the free margin of the valves, with newly formed blood vessels, is often thought to constitute evidence of old rheumatic infection. Especially prominent in old rheumatic heart disease is the increase in the number of vessels in the sub-endocardium and their penetration into the endocardium proper of the left atrium. The sub-endocardial elastic tissue is likewise commonly increased, often to a considerable degree. It is often thought that such changes, even in the absence of a clear-cut history of rheumatic fever, should be taken as evidence of a rheumatic etiology of old valvular lesions.

In general, however, we believe that in instances in which there is neither good clinical nor pathologic evidence of previous rheumatic disease caution should be exercised in the interpretation of valvular deformities. It would seem that in such instances more will be gained by withholding judgment and carrying on further investigation than by arriving at more or less dogmatic conclusions. We sometimes use the terminology "rheumatic type" to denote reasonable doubt as to a true rheumatic origin of the old endocarditis.

General Considerations. The healing of acute rheumatic endocarditis may leave no grossly demonstrable defect in form or function or may leave merely a slight thickening of the valve leaflets along the line of closure. The number of valves affected and the degree of scarring and deformity vary greatly with the number and severity of previous attacks as well as the age at which death occurs. The

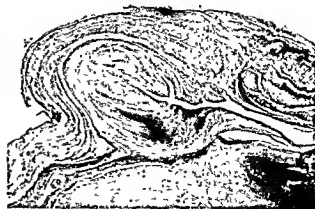
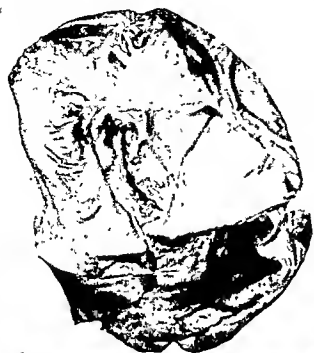


Figure IX-19. Chronic aortic valvulitis. Hematoxylin and eosin. X22. Compare with Figure IX-18a.



a



b

Figure IX-20. Stenosis of orifice of mitral valve.
a. Fusion and calcification of leaflets with stenosis of orifice.

b. Stenosis of mitral orifice and mural thrombi in left atrium.

valvular scars and deformities are for the most part the result of valvular inflammation and only in small part due to organization of vegetations. Organization of thrombi and contraction may be an important explanation of some deformities but the importance of cellular proliferation in the valve itself is often underestimated. The scar forms as a result of

fibroblastic proliferation and collagen formation; lipid deposition and calcification occur later.

General Incidence. Although not all valvular deformities are rheumatic in origin, it is generally agreed that most of them are. Of 73 cases in which old deformed valves were present, 55 were found to result from rheumatic endocarditis, and in 27 of these 55, incompletely healed rheumatic lesions were recognizable (Clawson and Bell, 1926). The greatest number of deaths resulting from rheumatic heart disease occur in the group of cases in which valvular deformities are present (73.5 per cent of 796 cases; Clawson, 1940a). According to Clawson, the incidence of involvement of each valve in 351 cases in which there were valvular deformities, was as follows: aortic alone, 21 cases; mitral alone, 214 cases; aortic and mitral, 73 cases; aortic, mitral and tricuspid, 25 cases; mitral and tricuspid, 16 cases; pulmonic valve, 1 case, and all valves, 1 case. These figures do not include 234 cases in which calcified nodular aortic lesions were found. In this latter group there were 92 cases in which aortic and mitral valves were involved and 5 cases in which aortic, mitral and tricuspid valves were involved.

Deformities of Mitral Valve. These are observed commonly in young and middle-aged persons and less commonly in the old. Girls and women show a greater tendency to deformity of the mitral valve than do males; the ratio is about 3:2 (White, 1951).

Mitral stenosis. Stenosis of the mitral orifice is the most common type of deformity. It results from fusion of the leaflets at their edges and fusion and shortening of the chordae tendineae. On examination from the open left atrium, this lesion has a characteristic diaphragmatic or funnel shape (Figure IX-20a, b). The walls of the funnel are formed by the fused leaflets of the valve which lead down to a small opening of variable shape. This opening has received such names as "buttonhole" or "fish mouth." Calcium salts, either diffusely distributed or deposited in nodular masses, are frequently present in the thickened leaflets. The latter sometimes erode

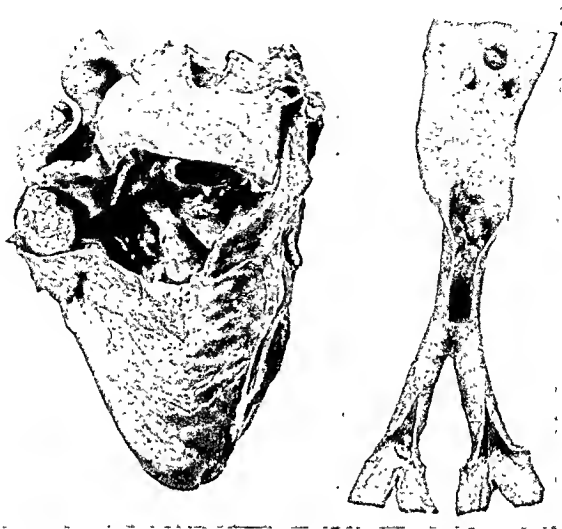


Figure IX-20c Stenosis of mitral orifice and thrombosis of left auricular appendage, producing embolism to abdominal aorta with resulting gangrene of both lower extremities. (WCCH, 39 A 38.)

the endocardium and are exposed to the blood stream. Sometimes there is calcification of the ring with or without simultaneous involvement of the leaflet. The leaflets may be so adherent and rigid that the movement necessary for their apposition is not possible. Consequently, valvular insufficiency is present, as well as stenosis of the orifice. According to White (1951), mitral stenosis and mitral regurgitation are almost invariably combined. In rare instances, however, one may occur without the other: (1) When retraction of the relatively undamaged or at least relatively nonadherent valve leaflets is caused by shortened, contracted and perhaps fused chordae tendineae, mitral regurgitation may occur without stenosis. (2) When the valve leaflets are fused at the commissures, stenosis of

the mitral orifice may occur without sufficient fibrosis or thickening of the extremities of the leaflets, or shortening of the chordae tendineae, to allow regurgitation. Pure stenosis (extreme stenosis with only slight insufficiency) was present in 37 of 95 cases of disease of the mitral valve reported by Clawson, Bell and Hartzell, in 1926. Severe degrees of rheumatic mitral stenosis are observed more frequently than severe degrees of mitral incompetence and are apparently borne better (White). The development of stenosis of the mitral orifice is a gradual process and the earliest defect in rheumatic children is insufficiency rather than stenosis. According to White, it requires at least 2 years for the development of mitral stenosis.

When stenosis of the mitral valve is present,



Figure IX-21. Fibrosing lesions causing mitral insufficiency.

the ring and leaflets are microscopically composed of dense fibrous tissue which is usually hyaline in appearance. All signs of active inflammation are absent except, occasionally, a little perivascular lymphocytic infiltration in the central part of the leaflets. There is extensive vascularization of the leaflet and annulus fibrosus by capillaries and extremely thick-walled vessels with narrow lumina.

Effects of mitral stenosis on the heart. In the presence of a stenotic mitral orifice the left atrium and the right ventricle reveal evidence of hypertrophy and dilatation. The left atrial enlargement may be so extreme that the heart may appear to be merely an appendage to an atrial aneurysm. These changes are, of course, the result of the increased effort required to force the blood through the narrowed mitral opening and past the resulting obstruction. The degree of stenosis alone probably does not account for such cases of extreme atrial enlargement but rather the combined effect of mitral regurgitation, mitral stenosis, the dilatation that comes with atrial fibrillation, and other factors not well understood. In 16 of a series of 26 cases of large left atria found at necropsy at the Massachusetts General Hospital, mitral stenosis was present and in 10, mitral insufficiency without stenosis was present (White, 1951).

Mural thrombi, particularly in the auricular appendage or atrium, are likely to form in the later stages of the disease when the atria fibrillate (Figure IX-20c). Pedunculated

thrombi and free or ball-thrombi are rarely found. When present, they may mechanically obstruct the circulation, causing marked feebleness of the pulse and syncope.

The right atrium eventually also may become hypertrophied and dilated if the right ventricular dilatation produces tricuspid regurgitation. The left ventricle may show no evidence of hypertrophy, even when the right ventricle and left atrium are double their normal size; in fact the left ventricle may be a little smaller than normal as a result of diminished work. The apex of the heart is sometimes formed in large part by the right ventricle.

Occasionally angina pectoris occurs in cases of uncomplicated mitral stenosis. According to Blackford (1940), this is the result of a failing heart muscle. The right ventricle and left atrium, which are taxed to force blood through the ste-



Figure IX-22. Pulmonary lesions in mitral stenosis.

a. Congestion, edema and fibrosis of alveolar walls. Hematoxylin and eosin. X 165.

b. Intimal fibrosis and medial hypertrophy of arteries. Elastin-van Gieson. X 125.

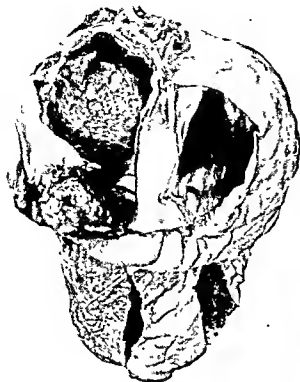


Figure IX-22c. Ball-valve thrombus in left atrium in heart with stenosis of mitral orifice. Dorsal view of heart (WCGH, 40 A 466.)

nosed mitral orifice, are unable to meet unusual demands, the left ventricle, therefore, is unable to sustain a high enough pressure in the root of the aorta to supply the coronary arteries with a sufficient amount of oxygenated blood.

Although the point is still disputed, a number of authors believe that the factor precipitating cardiac failure in patients who have old rheumatic heart disease is often reactivation of the rheumatic myocarditis (Rogers and Robbins, 1947).

A number of reports have appeared of finding of Aschoff bodies and structures resembling Aschoff bodies in the subendocardial regions of auricular appendages removed during commissurotomy for stenosis of the mitral orifice. Kuschner and associates (1952) found structures which they labeled Aschoff bodies in 4 of 11 specimens from the auricular appendage. McKeown (1953) found, in 24 of 53 such specimens, lesions which she believed showed the same distribution and structure as the Aschoff body. Luse and associates (1954) examined tissue surgically excised from the left auricular appendage from 77 patients who had undergone mitral commissurotomy, and found Aschoff bodies in 32 (41.6 per cent). The bodies were most prominent in the

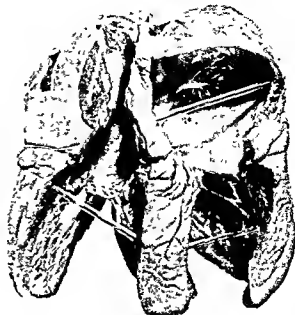


Figure IX-22d. Stenosis of orifice of mitral and tricuspid valves. Dilatation of right atrium. Obstructing mural thrombus of left atrium which was responsible for cyanosis. Heart viewed dorsally. (WCGH, 33 A 4)

endocardial and subendocardial tissues and their incidence was lower among older patients. Clark and Anderson (1955) found histologic evidence of rheumatic activity in the form of Aschoff nodules in 55 per cent of patients, although there were no signs of clinical activity of acute rheumatic fever. Microscopically, the granulomatous lesions were described as "largely characteristic Aschoff nodules." They showed a central nidus of fragmented and swollen collagen fibers, surrounded by loose connective tissue, with numerous large dark-staining mononuclear and multinucleated Aschoff cells, small round cells and occasional polymorphonuclear leukocytes. (See also Tedeschi *et al.*, 1955.)

The question is, of course, whether these structures are true Aschoff bodies. Unquestionably, occasionally a patient who has had a mitral commissurotomy may shortly before the operation have had an attack of recurrent acute rheumatic fever which was clinically unrecognized. From the illustrations accompanying the reports, we seriously doubt that some of the depicted lesions are true Aschoff bodies. Enticknap (1953) found lesions confined to the endocardium which he called "probable" Aschoff bodies, admitting that some of these resembled but were not typical Aschoff bodies.

Elster and Wood (1955) found no good cor-

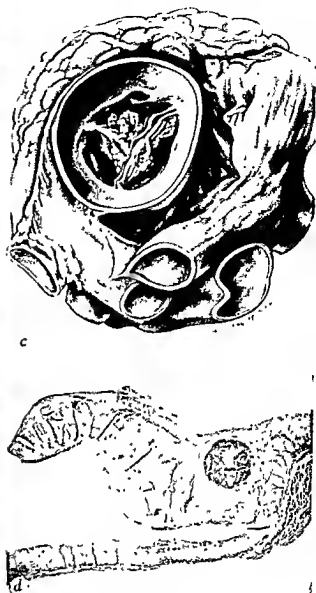
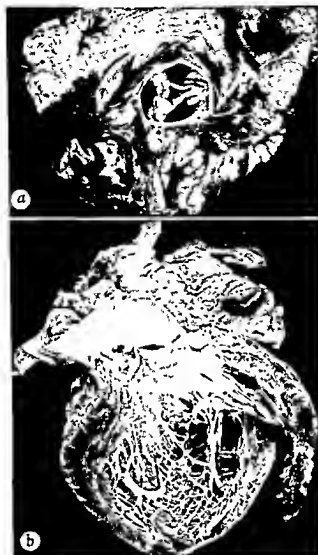


Figure IX-23. Deformities of aortic valve.

a. Stenosis of aortic orifice.

b. Aortic insufficiency with regurgitant (diastolic) endocardial pocket in lower portion of figure.

c. Calcific sclerosis with bicuspid formation of aortic valve. (Drawing by Louise Horne, Wayne County General Hospital, WCGH, 45 A 160.)

d. Fibrosis and calcification. Hematoxylin and eosin. X7.

relation in the values of C-reactive protein in the blood serum with the finding of Aschoff bodies in the left auricular appendage of patients who have had mitral commissurotomy.

Mitral insufficiency. Since stenosis of the orifice and insufficiency of the valve are generally combined to a greater or lesser degree in cases of rheumatic mitral disease, the effects on the heart depend in part on the relative amounts of stenosis and regurgitation and in part on the absolute degree of valvular disease. If mitral insufficiency is the chief defect (Figure IX-21), hypertrophy of the left ventricle occurs as well as enlargement of the

left atrium and right ventricle. The posterior wall of the left atrium also may reveal focal thickening of the endocardium or cusplike lesions which result when a regurgitant blood stream strikes these points (so-called jet lesions; Edwards and Burchell, 1958). Later there may be hypertrophy and dilatation of the right atrium. With severe and long-standing mitral insufficiency, the size of the heart may become enormous.

Aside from hypertrophy, the heart muscle in deformities of the mitral valve may be normal, or there may be perivascular scars suggestive of healed Aschoff bodies. In cases

of valvular deformity of long standing, the myocardium may become exhausted and fail without evidence of pathologic change, unless there is a complication such as recurrence of rheumatic inflammation, bacterial endocarditis or serious disease of the coronary arteries. It is frequently the valvular lesion and not the myocardial disease that eventually causes failure and death.

Effects of mitral deformities on other organs.

In the presence of mitral deformities, the lungs and later the liver and other organs, reveal evidence of chronic passive hyperemia. The distended pulmonary capillaries and bronchial veins (Ferguson *et al.*, 1944) may rupture, giving rise to hemoptysis. Areas of hemorrhage and infarction are found particularly at the bases of the lungs, and phagocytes filled with hemosiderin form a prominent feature of the histologic appearance. When deposits of iron pigment are sufficiently extensive, the lungs have a brown hue and the condition is known as brown induration of the lung. Parker and Weiss (1936) pointed out that, in addition to engorgement and thickening of the walls of the capillaries and arterioles, permanent changes in structure occur in the alveolar walls (Figure IX-22a), which may become twenty times thicker than normal. The basement membrane of the capillary endothelium becomes thickened and separated from that of the alveolar epithelium by interstitial edema and collagen. There is intimal thickening of the pulmonary arteries with hyperplastic arteriolar sclerosis (Figure IX-22b). All these changes seriously restrict gaseous interchange so that intense cyanosis may persist in spite of myocardial improvement.

Deformities of Aortic Valve. The changes that may occur as a result of repeated attacks of rheumatic inflammation have already been described under recurrent and chronic valvulitis. Suffice it to state here that adhesions of the cusps at the commissures, thickening, fibrosis and calcification of the ring and cusps lead to stenosis of varying degrees (Figure IX-23a, c). Scarring, retraction and stiffening of the free borders of the cusps, however, result in insufficiency or regurgitation (Fig-

ure IX-23b, d) of the aortic valve; here also rheumatic inflammation causes both stenosis and regurgitation; it rarely leads to regurgitation alone except in the earliest stages, and also rarely causes stenosis alone. The end result of repeated attacks of rheumatic disease may be preponderant aortic stenosis, preponderant aortic regurgitation or equal degrees of both (White, 1951).

In Cabot's series (1926) of 152 cases of aortic valvular disease there were 93 cases of stenosis and regurgitation of the aortic valve of rheumatic origin, and 11 cases of regurgitation with little or no stenosis, of which only 6 proved to be of rheumatic origin. Most of the cases with aortic regurgitation without stenosis were syphilitic in origin (44 cases). In a group of 130 cases of old valvular defects studied by Clawson and associates in 1926, 41 revealed combined stenosis of the orifice and insufficiency of the aortic valve. In 13 of these 41 cases insufficiency was the dominant defect.

Aortic stenosis. According to Clawson and associates (1938), aortic stenosis is a common form of heart disease. It comprises 40 per cent of all deformities of the valves. It occurs chiefly in males in a ratio of 4:1 (Dry and Willius, 1939). The average age at death is 15 to 20 years more than in cases of mitral stenosis. The usual form of aortic stenosis is the calcific nodular type. The orifice is reduced to a narrow rounded or triangular opening and the cusps contain massive calcified nodules (calcified aortic stenosis). The calcified masses usually are found on both surfaces of the cusps. Occasionally they are observed only on the aortic surface and rarely only on the ventricular surface. Microscopically the deposits of calcium are usually associated with a proliferative type of inflammatory process which is not always in immediate relation to the location of the calcium. Often the most pronounced inflammation is seen in parts of the scar where there is no calcium. The calcium is usually embedded in scar tissue near thick-walled vessels. Vascularization of the valve and the ring is usually observed. Muller (1956) found isolated aortic stenosis in 35 per cent of his cases of cicatricial valvular disease.

It is at times extremely difficult to make a decision concerning the etiologic factor in cases of aortic stenosis. When the lesion is associated with a clear-cut history of rheumatic fever or with a deformity of the mitral valve, rheumatic inflammation appears likely. When it is not associated with other valvular deformities, some investigators (Monckeberg, 1904; Solvol and Gross, 1936; Ashworth, 1916; Holtgren, 1948) have concluded that degenerative or metabolic factors are responsible. Solvol and Gross, and Holtgren were unable to find stigmata of rheumatic fever in most of the hearts with calcific disease of the aortic valve. According to Ashworth, the factors to be considered in the development of atherosclerosis of the heart valves are age, hypertension, the physiologic decrease in elasticity of the annulus fibrosus of the aortic and mitral valves, and the effect of tension and vibration on certain portions of the valves. Other investigators (Hall and Ichioke, 1940; Karsner and Koletsky, 1917) have concluded that rheumatic inflammation is always the basis of the deformity. This assumption is based on the incidence of rheumatic fever in the history of patients with this deformity, the numerous transitions found between undoubtedly healed rheumatic lesions and calcified nodular valves, and the association of other lesions also probably caused by rheumatic fever.

Barr and associates (1954) described an instance of familial hypercholesteremic xanthomatosis in a young adult with extensive atherosclerosis of the aorta and a severe calcific stenosis of the aortic valve. There were no rheumatic stigmata. Thus it seems that calcific aortic stenosis may likewise have an atherosclerotic basis.

Our views on this problem have been indicated in the general considerations of the subject of valvular deformities. It seems that, although calcific disease of the aortic valve in most cases is rheumatic in origin, knowledge of the early stages of this deformity is not complete enough to permit one to regard rheumatic injury as responsible for this condition in all cases.

Bicuspid aortic valve may be congenital or the result of inflammation, most often rheu-

matic. In either instance, calcific stenosis may be superimposed. Karsner and Koletsky (1917) maintained that if the raphe remains at the base of the sinus of Valsalva, the bicuspid aortic valve is the result of a congenital anomaly; however, if it equals the cusp in height, it is acquired and the result of an old endocarditis, most likely of rheumatic origin.

Effect of aortic stenosis on the heart. In cases in which aortic stenosis is not associated with regurgitation, the left ventricle is tremendously hypertrophied and there is little or no dilatation until the heart has begun to fail. The right ventricle may appear to be a mere appendage to the left; the wall of the latter bulges markedly into the cavity of the former. The other chambers of the heart are unaffected until cardiac failure sets in and then dilatation of the right side of the heart will occur. The degree of atherosclerosis of the ascending aorta and coronary arteries varies inversely with the degree of aortic stenosis. This suggests that the stenosis develops early in life and protects the aorta against the normal fluctuations of blood pressure.

Cause of death in aortic stenosis. Aortic stenosis is apparently better tolerated than other varieties of valvular deformity. Although severe stenosis of the aortic orifice is a serious burden on the heart, it is a lighter one than aortic regurgitation. This is indicated by the fact that in most cases, both clinically and at autopsy, aortic stenosis is encountered in persons who are relatively old.

Death is associated with congestive failure in about one-third of the cases. Sudden death occurs in about one-fifth of the cases and when all grades of stenosis are considered, death seems to result from noncardiac causes in about one-half of the cases (Dry and Williams, 1939).

Although coronary occlusion is extremely rare, angina pectoris is a symptom in 19 per cent of cases, according to McGinn and White (1934), and in 22.7 per cent, according to Contratto and Levine (1937). This symptom has been explained as being the result of myocardial ischemia. The latter has been attributed to the ste-

notic orifice, the increase in cardiac work and also to vasomotor changes in the caliber of the coronary vessels (Harrison, 1937). Contratto and Levine have pointed out the likeness of the aorta and coronary system in these cases to the common water-faucet suction pump and have suggested that the negative pressure produced may interfere with coronary flow.

Disturbances in atrioventricular conduction also are often associated with calcific aortic stenosis (Boas, 1935). These are the result of an extension of the calcific process into the annulus fibrosus or ventricular septum. Associated mitral stenosis seriously militates against maintenance of cardiac function in cases of aortic stenosis.

Aortic insufficiency. Insufficiency results when there is curling and retraction of the cusps. Marked aortic regurgitation has a more rapidly serious effect than marked aortic stenosis. The heart becomes very large and left ventricular hypertrophy and compensatory dilatation apparently develop simultaneously. Hearts which weigh 1000 grams or more have been observed. The largest and heaviest hearts generally occur in the presence of pure aortic regurgitation. The regurgitation is most often a complication of syphilitic aortitis but occasionally results from rheumatic infection. When the left ventricle dilates tremendously as a result of aortic regurgitation, the mitral valve becomes incompetent, and hypertrophy and dilatation of the left atrium ensue. These are followed in turn by enlargement of the right ventricle and eventually by enlargement of the right atrium too, although death from left ventricular failure is likely to interrupt the full evolution of these various steps (White, 1951). In addition to the extensive hypertrophy and dilatation with flattening of the trabeculae carneae, endocardial pockets and focal thickening also may result from the regurgitant blood stream (Figure IX-23*b*); aside from these changes, the myocardium may reveal no lesion.

Apparently the hypertrophied muscle fails under the strain of overwork which is caused by the valvular deformity. Another factor in bringing about myocardial failure may be the low diastolic pressure which, in turn, is the result of the aortic insufficiency. Normally the coronary circulation is maintained by a sufficient diastolic pressure.

The frequent occurrence of angina pectoris in cases of advanced aortic stenosis also suggests the importance of functional coronary insufficiency. Aside from focal fibrosis of the myocardium, however, there is usually no morphologic evidence of myocardial ischemia. Dilatation of the ascending aorta occurs but is not as common in cases of rheumatic aortic regurgitation as it is in cases of regurgitation resulting from syphilitic valvulitis and aortitis.

Deformities of Tricuspid Valve. Evidence of inflammation can be found as frequently in the tricuspid valves as in the mitral and aortic valves (Gross and Friedberg, 1936). Deformities of the tricuspid valve, however, are rare and seldom occur without lesions in other valves. Among 4300 necropsies performed at the Massachusetts General Hospital, 217 cases of rheumatic heart disease and only 47 lesions of the tricuspid valve were described. Only 30 of these 47 lesions were tricuspid stenosis of sufficient degree to be regarded as of clinical importance (Cooke and White, 1941). In a study of 351 cases of old valvular deformities (Table IX-2), Clawson was unable to find a single instance in which the tricuspid valve alone was involved. It was involved, however, in 42 cases in association with other valvular lesions. The age and sex incidence of the patients whose tricuspid valves were deformed corresponded roughly to those of patients who have mitral stenosis. Children and young adults were affected, and females were affected slightly more frequently than males. The average age at death was much less than that in all cases of rheumatic heart disease. In Cooke and White's series it was 23 years as compared with 42 years for rheumatic heart disease in general. Laake (1958) reported tricuspid stenosis in 20.4 per cent of 54 persons with rheumatic heart disease at autopsy. However, in only 1 instance was tricuspid stenosis diagnosed clinically.

Valvular insufficiency and stenosis of the orifice are almost invariably associated with deformities of the tricuspid valve, although one or the other may predominate. According to White, stenosis becomes of clinical importance when the circumference of the adult tricuspid ostium (normally 11 to 13 cm.) is reduced to 8 cm. or less (Figure IX-24*a, b*).

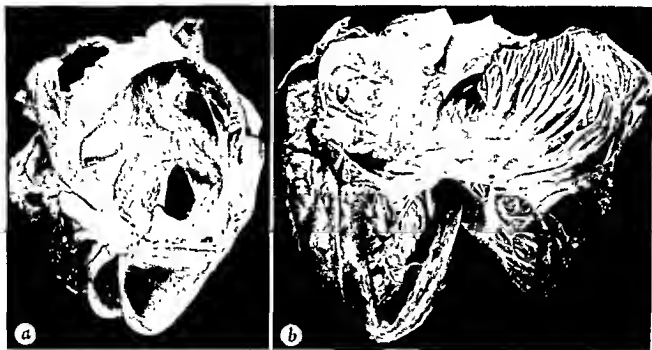


Figure IX-24. Deformities of tricuspid valve. *a* Insufficiency with stenosis of orifice. *b*. Stenosis of tricuspid orifice (valve opened).

Functional tricuspid insufficiency is common in association with right ventricular dilatation associated with congestive heart failure, and is rarely associated with other factors like anemia and pulmonary insufficiency.

Effect on the heart. Because deformities of other valves are practically always associated with deformities of the tricuspid valve, a combination of effects is noted on the cardiac chambers. Well-marked tricuspid stenosis, if uncomplicated, naturally affects little of the heart except the right atrium which becomes enlarged. Tricuspid stenosis acts wholly on the circulation as a process obstructing the return of blood to the heart and is comparable to the effect of chronic constrictive pericarditis. Tricuspid insufficiency results in hypertrophy and dilatation of right atrium and ventricle.

According to Cooke and White, the presence of deformity of the tricuspid valve signifies a more severe degree of heart disease than deformity of the mitral or mitral and aortic valves and consequently death comes much earlier. However, after systemic venous congestion sets in, life lasts longer when stenosis of the tricuspid orifice is present than when it is not, because of the protection afforded to the heart and lungs by

the mechanical obstruction of the stenosis. Consequently tricuspid stenosis is similar to chronic constrictive pericarditis in that it produces a cardiac invalid who may live for years; he may have little dyspnea despite hepatic enlargement and ascites. This long course contrasts with the shorter course of life in cases of pure mitral stenosis after congestive failure has set in.

Deformities of Pulmonary Valve. Acute rheumatic inflammation of the pulmonary valves (Figure IX-12), occurs not infrequently (Cross and Friedberg, 1936) in association with involvement of other valves, but apparently leads to deformity only rarely (2 cases out of a total of 351 cases of valvular deformities reported by Clawson, 1940a). As a result of deformities of the pulmonary valve, hypertrophy of the right ventricle, and later, dilatation with signs of congestive failure develop. The right atrium also is usually enlarged.

Mural Endocarditis

Lesions of the mural or parietal endocardium in rheumatic fever are seen most commonly in the left atrium. Although these lesions had been previously noted and described (Huchard, 1903; Harper, 1914; Hertel, 1920),

they did not attract much attention until MacCallum's classic description in 1924.

Lesions of the Left Atrium. Incidence. Von Glahn (1926) found these lesions in 9 (29 per cent) of 31 cases, Thayer (1925) in 10 (40 per cent) of 25 cases, and Gross (1935b) in 70 (80 per cent) of 87 cases.

Gross appearance. The lesion of mural endocarditis is usually observed just above the posterior leaflet of the mitral valve. It is usually about 3 cm. in greatest extent but may involve almost the entire endocardial surface and extend into the auricular appendage and up to the orifices of the pulmonary veins. The wall of the atrium is markedly thickened and made irregular by low ridges and hillocks separated by furrows with no definite pattern (Von Glahn). Occasionally the irregular furrowed appearance is absent and there are only flat, often rounded, plateaus sometimes measuring no more than 2 mm. in diameter (Gross). On rare occasions, distinct projections may be seen which resemble vegetations. In cases of acute mural endocarditis, the lesion has a tawny gray color; it is grayer and more translucent in the older lesions. In these older lesions the patch may appear dense and scar-like. It rarely is calcified (Stewart and Branch, 1924).

Histologic appearance of acute lesions. In these lesions, as in the acute valvulitis, the inflammatory process consists of characteristic and noncharacteristic components. The characteristic components consist of more or less typical Aschoff bodies which seem to have a predilection for the subendocardial layers. Usually these structures are forced into bands or rows of palisaded cells on either side of swollen collagen fibrils in various stages of fibrinoid degeneration (Figure IX-25a, b). The nuclei are arranged perpendicularly to the altered collagen and the appearance is like that observed in some instances in the valve leaflets. Frequently the band of fibrinoid degeneration coincides with the layer of connective tissue immediately beneath the endothelium. In some instances there is fibrinoid degeneration of the subendothelial connective tissue without any cells or with only a few cells arranged about it.

Among the indications of nonspecific inflammation are edema and marked infiltration of mononuclear cells, mostly lymphocytes. Polymorphonuclear cells, including the eosinophilic variety, are present occasionally, and rarely polymorphonuclear cells may be predominant in the inflammatory exudate. These cellular aggregations are found in any portion of the endocardium but are perhaps more often present in the inner half. They separate and distort the elastic fibers and are often the cause of the ridges and hillocks on the endocardial surface. The endothelium over the sites of these changes is frequently intact. When the endothelium has ulcerated, there is a thin layer of fibrin on the surface and occasionally this fibrin is collected in verruca-like vegetations (Figure IX-26).

Histologic appearance of chronic lesions. Healing and repair take place readily. Capil-

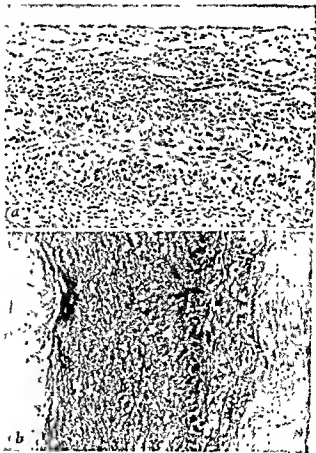


Figure IX-25. Lesions of mural endocardium.

a. Bandlike zone of fibrinoid degeneration with palisaded basophilic cells. Hematoxylin and eosin, X 135.

b. Healed stage. Increased collagenous and elastic fibrils. Elastin-van Gieson, X 95.

laries surrounded by varying numbers of lymphocytes and mononuclear cells penetrate to the outer half of the endocardium. Fibroblastic proliferation and fibrosis may be present, as well as an increase of delicate, distorted elastic fibrils. As healing progresses, the characteristic cells and Aschoff bodies disappear and finally a dense avascular scar is all that is left in the superficial part. In the deeper layers near the myocardium, small collections of lymphocytes persist for a long time. Calcium frequently is deposited in the superficial portion of the endocardium where the scar is located. It may appear in thin plates or small nodular clumps.

Other Mural Endocardial Lesions. Aside from the characteristic lesions which appear in the left atrium, the mural endocardium

may be involved as an extension of the inflammatory process from the valves, valve rings and chordae tendineae. These lesions are particularly common in the subvalvular angles of the aortic valve, in the septum fibrosum (Gross and Friedberg, 1936) and on the papillary muscles of the left ventricle. Except for these lesions, involvement of the mural endocardium in rheumatic fever is not common. Von Glahn and Pappenheimer (1926) found involvement of the endocardium of the right atrium in only 3 of 109 cases. In each of these cases the lesion was situated at the margin of the fossa ovalis. In 2 of them, chains of characteristic verrucae were present and in the third, a somewhat larger vegetative process was noted.

PERICARDITIS

Incidence. Coombs in 1924 found a progressive decrease in the incidence of pericardial lesions, from 100 per cent of patients who had rheumatic carditis and died in the first decade of life to 25 per cent of those who died in the fourth or subsequent decades of life.

According to Coombs, the lower incidence in the later age periods indicated that these patients suffered from milder lesions and, therefore, survived longer. Friedberg and Gross (1936) found microscopic evidence of pericarditis in 100 per cent of cases of acute and recurrent rheumatic carditis and in 85 and 75 per cent, respectively, of cases of chronic and healed rheumatic carditis. Clawson (1940a) found pericarditis in 52.5 per cent of the cases of acute rheumatic endocarditis, in 41.1 per cent of cases of recurrent rheumatic endocarditis and in 12.5 to 22.2 per cent of cases in which various types of valvular deformities were present.

Acute Pericarditis

Gross Appearance. In gross appearance, acute rheumatic pericarditis differs but little from acute pericarditis of any other type, except that the exudate is predominantly fibrinous and rarely serous or frankly purulent (see Chapter X on Pericarditis). Consequently, the amount of fluid in the pericardial sac is likely to be less than in some other varieties of



Figure IX-26. Lesions of left ventricle. Hematoxylin and eosin.

a. Mural endocarditis. X 135.

b. Verruca of endocardium. X 145.

acute pericarditis. In cases of early and mild rheumatic pericarditis, all that may be seen is a roughening and reddening of the serous surfaces, often limited to one or two patches. These early lesions may be observed most readily on the visceral surface of the pericardium, particularly at the roots of the vessels and over the atrial appendages. In the presence of well-developed pericarditis, it may be difficult to open the pericardial sac because it is filled with a thick mat of pink fibrin which is firmly adherent to the serous surfaces (Figure IX-27). A slightly turbid fluid usually oozes from the fibrin, and distinct loculi may be filled with fluid within the fibrin, but it is unusual to find effusion of fluid in rheumatic pericarditis of sufficient quantities to require instrumental evacuation (Coombs, 1924). If the fibrin is removed, the serous surface is found to be rough, reddened and sometimes hemorrhagic. Both pericardial layers are thickened and sometimes this thicken-

ing is of a nodular character. The external surface of the parietal pericardium is often bound to the adjacent pleural surfaces by fibrinous adhesions.

Histologic Appearance. The histologic appearance of acute rheumatic pericarditis is similar to that presented by acute inflammation of any serous membrane, except for the association of certain lesions which have come to be regarded as specific for rheumatic fever (Klinge, 1933). In pericarditis the latter lesions are more frequently overshadowed by the acute inflammatory process than in any other rheumatic lesion. The surface of the pericardium is covered by fibrin in the meshes of which there are usually a few, but rarely many, leukocytes including polymorphonuclear leukocytes and occasional histocytes. The lining cells on the surface may be intact, but more frequently they show evidence of proliferation and, in more severe cases, of desquamation. Not infrequently the meso-

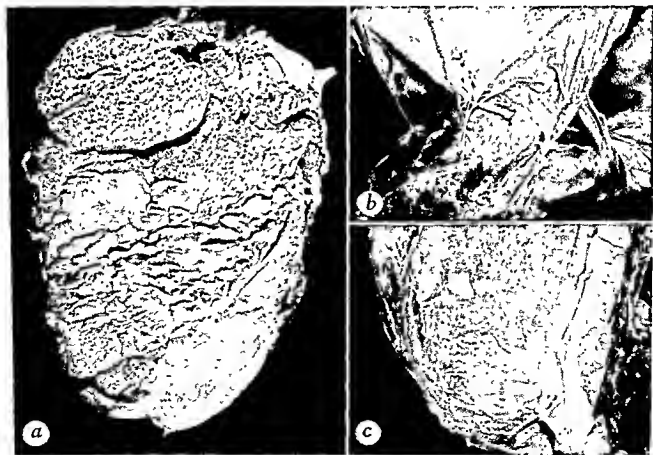


Figure IX-27. Pericarditis in rheumatic heart disease. *a*, Acute fibrinous pericarditis. *b*, Chronic adhesive pericarditis. *c*, Epicardial scar.

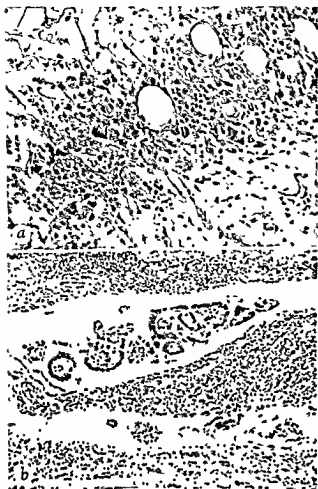


Figure IX-28. Pericarditis in rheumatic heart disease. Hematoxylin and eosin.

a. Granuloma in epicardial fat. X 200.

b. Pseudoglandular proliferation of epicardial cells. X 120.

thelial cells desquamate in strips and appear as bizarre pseudoglandular formations (Figure IX-28b). Occasionally the cells proliferate without desquamating and form cystic or solid polypoid structures (Friedberg and Gross, 1934, 1936). In the subepicardial tissue there is usually a diffuse exudate which consists mainly of lymphocytes and plasma cells with an occasional polymorphonuclear leukocyte. Vascularization by dilated capillaries is pronounced and, even in the early cases, there may be beginning organization of the fibrin by fibroblasts and capillaries. Frequently the smaller vessels, including the capillaries, reveal swelling and proliferation of the endothelium.

In addition to these nonspecific signs of inflammation, there are usually foci of fibrinoid degeneration in the connective tissue

together with associated collections of characteristic, large cells with basophilic cytoplasm (Figures IX-28 and IX-29). These circumscribed nodules are usually more diffuse and irregular than the corresponding structures in the myocardium. Foci of fibrinoid degeneration of collagen with little or no characteristic cellular reaction may be observed more frequently in the pericardium than in any other site in the heart (Figure IX-28a). Occasionally there is palisading of Aschoff cells and fibroblasts around foci of fibrinoid degeneration or along a necrotic layer of collagen on the surface. There are no characteristic Aschoff bodies.

Recurrent Pericarditis

Gross Appearance. This varies considerably with the number and severity of previous attacks of pericardial inflammation and the extent of the recent attack. In all cases a marked thickening of pericardial membranes and an almost universal formation of adhesions are noted. The adhesions tend to obliterate the pericardial cavity. In addition to these evidences of older inflammation, there is also fresh exudation of a largely fibrinous exudate. Portions of the older exudate may appear red as a result of extensive vascularization.

Histologic Appearance. In addition to the signs of an older subsiding or healed nonspecific inflammation, there is evidence of recent inflammation such as foci of fibrinoid degeneration of the collagen and associated collections of characteristic cells. These granulomatous foci are often better developed in recurrent than in acute pericarditis. Nonspecific signs of recent inflammation, in the form of collections of mononuclear and polymorphonuclear cells, also may be observed.

Chronic and Healed Pericarditis

Gross Appearance. Rheumatic pericarditis may leave as its only mark one or two opaque white patches of thickened epicardium, known as milk spots, or it may leave only a few fibrous tags of no great importance (Figure IX-27). On the other hand the number and extent of pericardial adhesions may

be sufficient to obliterate the entire sac. In addition to these intrapericardial adhesions, extrapericardial lesions bind the sac to the mediastinal tissues, lungs and the chest wall. Calcium salts may be deposited in these adhesions and occasionally the heart may be partially surrounded by a solid wall of such depositions. The entity "constrictive pericarditis" sometimes resulting from rheumatic injury is discussed elsewhere (see Chapter X on Pericarditis).

Histologic Appearance. The thickened walls

of the pericardial sac are extensively scarred with a mild inflammatory type of lesion having collections of lymphocytes in the inner layers. Vascularization by thickened vessels and capillaries is often extensive. There is no evidence of fibrinous exudation or other evidence of acute inflammation. The mesothelial lining may be intact or replaced by fibrous adhesions. Deposits of calcium may be observed in the dense connective tissue. For the effects of pericardial adhesions on the myocardium, see Chapter X on Pericarditis.

LESIONS OF BLOOD VESSELS

Aorta

Involvement of the aorta in rheumatic fever has been recognized and accepted since the systematic histologic study by Klotz in 1912. All portions of the vessel may be involved but the lesions are apparently more numerous in the ascending and thoracic portions (Klotz, 1912, Klinge, 1933). According to Gross (1935a), the aortic and pulmonic roots display a strikingly high incidence of destructive and inflammatory lesions, consisting of scarring, disruption of elastic tissue, vascularization and other inflammatory phenomena. Studies of the incidence of the lesions throughout the aorta have not been made, but Klinge stated that involvement of the aorta is the rule rather than the exception.

Gross Appearance. Grossly the lesions have been described as nodular fibrous thickenings by Klotz in 1912, as elevated, almost transparent, plaques and ridges of brown color by Von Glahn and Pappenheimer in 1926; as soft, flat, glassy cushions by Klinge in 1933, and as yellow elevated nodules and streaks by Moore in 1946. In cases of chronic rheumatic disease, Klotz noted a great loss in elasticity of the entire wall and the vessel was thicker and heavier.

Histologic Appearance. *Adventitia.* In cases of acute involvement of the adventitia, there is congestion of the adventitial vessels with edema and marked infiltration of leukocytes, most of which are lymphocytes. The cellular elements are diffusely scattered throughout the adventitia but tend to be

concentrated about the vessels. The foci of fibrinoid degeneration generally are associated with the veins and arteries, which may or may not be involved (Figure IX-30). They



Figure IX-29. Pericarditis in rheumatic heart disease.
a. Fibrinoid change of ground substance. Mallory's phosphotungstic acid. X 90.
b. Granuloma in epicardial fat. Hematoxylin and eosin. X 60.



Figure IX-30. Vascular inflammation in heart disease. Hematoxylin and eosin.

a. Arteritis showing edema and vacuolization of muscle cells. X 290.

b. Arteritis in granulomatous stage. X 180.

c. Phlebitis with granulomatous inflammation of wall. X 115.

are generally larger and less clearly demarcated than the corresponding lesions in the myocardium (Klinge, 1933). In the granulomatous stage of the inflammatory process, the characteristic basophilic cells are found either

in the middle or at the borders of the foci of fibrinoid degeneration, and giant cells are scarce. In cases of chronic and inactive involvement a nonspecific type of perivascular inflammation may be observed but true Aschhoff bodies probably do not develop. The adventitia is greatly thickened by collagenous tissue and the walls of the nutrient arteries are thickened.

Media. In the acute stage of rheumatic fever, the arterioles are more prominent than usual and penetrate beyond the outer third of the media. Perivascular edema and numerous lymphocytes and plasma cells may be observed. The muscle elements in the neighborhood of the vasa vasorum often have disappeared. Circumscribed rheumatic nodules are not observed but there are foci of fibrinoid degeneration and necrosis which appear in rows. Large basophilic cells are present about the vessels; these also are frequently arranged in rows, apparently as a result of the arrangement of elastic fibers. In inactive and healed lesions, there is a marked increase in the number and size of the capillaries, scarring and disruption of elastic fibers. The scars are prominent and have been described as flame-shaped, oval and moth-eaten (Friedberg and Gross, 1936). They are perivascular in distribution and do not involve the entire thickness of the media as in syphilis.

Intima. In this layer, lesions are observed which are comparable to those in the atrial endocardium (Von Glahn and Pappenheimer, 1926). There are bands of fibrinoid degeneration of collagen and elastic tissue about which there are large basophilic cells, some of which are multinucleated, and some polymorphonuclear leukocytes. Formation of verrucae is rarely observed. In the healed stage, the lesion becomes converted into a scar which is difficult if not impossible to differentiate from ordinary aortic sclerosis.

Although the intimal lesions frequently occur alone, the adventitial and medial lesions usually occur together. It has been postulated, therefore, that the injury to the outer coats comes through the vasa vasorum, whereas the intimal injury comes from the blood in the aorta (Klinge, 1933).

According to Von Glahn and Pappenheimer, the rheumatic lesions can be distinguished from those of syphilis in that the former are restricted to the neighborhood of nutrient vessels and are not accompanied by the production of vascular granulation tissue. The cellular constituents are not as numerous; they differ from those observed in syphilitic aortitis and there is no evidence of gummatous necrosis.

Coronary Arteries

In this section, involvement of the adventitia of the smaller branches, which is a site of predilection for the myocardial rheumatic nodule, will not be discussed but involvement of the media and intima of the larger branches will be considered particularly. In these vessels, inflammation of varying degree occurs in about one-third of the active cases of rheumatic fever. The lesions of rheumatic fever in these vessels consist of edema, exudative and necrotizing inflammatory changes, fibrinoid degeneration, palisade formation, verrucous endarteritis and thrombi (Gross, Kugel and Epstein, 1935). Except when Aschoff bodies are a part of the inflammatory process, the lesions are not specific for rheumatic fever. Destruction of elastic fibers seems to be especially severe. According to Klinge, the fibrinoid degeneration of the ground substance and the lymphocytic and leukocytic exudation often are more pronounced than the proliferation and hypertrophy of the connective tissue cells. Also, according to him, longitudinal sections of the coronary arteries reveal a palisade arrangement of cells of the wall, such as has been described in the atrial and aortic lesions. Fibrosis of the coronary arteries occurs more frequently, more extensively and considerably earlier than in non-rheumatic control cases. Although these changes have not been shown to result from acute inflammatory lesions, it is practically certain that severe myocardial injury is associated with the disease in the coronary arteries (Karsner and Bayless, 1934).

Other Vessels

Lesions of small peripheral arterioles and

capillaries occur in various locations including the lungs (Von Glahn and Pappenheimer, 1928; Paul, 1928). Sloughing of the endothelium as a result of exudation of fibrin into the wall, necrosis of the cellular constituents and fragmentation of the elastic lamellae, have been described. In the perivascular tissue there is an exudate consisting of polymorphonuclear cells, radially arranged mononuclear cells and an outer loose infiltration of lymphoid and plasma cells and occasional eosinophils and fibroblasts. In this perivascular tissue are many dilated hyperemic capillaries which may extend far beyond the area of cellular infiltration. Thrombosis is not observed in these vessels. The acute lesions are followed by organization with or without formation of new collateral channels within the thickened intima and occasionally within the muscular layer. The lesions resemble most closely those of periarteritis nodosa but differ from these in the absence of thrombosis, the small size of the involved vessels, and the absence of nodules or aneurysmal formations. Identical changes have been described in pulmonary arterioles by Von Glahn and Pappenheimer as well as by Paul. Rheumatic lesions in the veins occur (Figure IX-30c) and have been studied extensively by Klinge (1933).

Relation to Other Similar Vascular Disease

As Karsner and Bayless (1934) have pointed out, it is difficult to orient the vascular lesion of rheumatic fever in the whole group of arterial diseases.

Aschoff (1906), Ophuls (1923), Friedberg and Gross (1934), Neale and Whitfield (1934), Middleton and McCarter (1935) and Pagel (1951) have stressed the close relationship between periarteritis nodosa and rheumatic fever. Friedberg and Gross, in particular, were of the opinion that rheumatic fever was a common cause of the vascular lesion termed "periarteritis nodosa." Fahr in 1920 suggested that rheumatic arterial disease may be a causative factor in malignant sclerosis and in 1921 drew attention to the resemblance between the arterial lesions of rheumatic fever, polyarteritis nodosa and dermatomyositis. Klinge (1933) and Vaubel (1932) discussed periarteritis nodosa, malignant sclerosis, certain forms

of cardiovascular sepsis, thromboangitis obliterans, focal glomerulonephritis and rheumatic fever in the same group on the basis of hyperergic causes. Semsroth and Koch (1930) as well as Metz (1931) were of the opinion that the arterial lesions of acute infectious disease, rheumatic fever and polyarteritis nodosa are manifestations of the allergic state which differ only in degree of involvement.

Methods capable of producing lesions re-

sembling periarteritis nodosa in animals, also produce lesions simulating those of rheumatic fever (Rich and Gregory, 1943; Selye and Pentz, 1943; Selye, 1946, 1947). It is obvious that more work along this line of investigation is necessary before a final conclusion can be reached concerning the relation of rheumatic vascular lesions to those of periarteritis nodosa.

LESIONS RESEMBLING THOSE IN RHEUMATIC FEVER

The occurrence of nodules in cases of subacute bacterial endocarditis similar or identical to those observed in cases of rheumatic fever is mentioned in the section on Endocarditis. The occurrence of lesions in cases of scarlet fever, similar to those of rheumatic fever, has been commented on in the discussion of the specificity of the Aschoff body. The occurrence of rheumatic-like lesions in syphilitic aortitis, reported by Clawson (1929), need not be considered further because the demonstration of the etiologic agent and the other characteristic features of the

latter disease usually are sufficient so that the differential diagnosis can be made without difficulty. The rare occurrence of rheumatic-like lesions in meningococcal endocarditis (Rhoads, 1927) or typhoid fever (Romberg, 1894) likewise offers no serious problems. The occurrence of rheumatic lesions in cases of rheumatoid arthritis, however, has aroused considerable interest because of the long-standing problem concerning the possible relationship of the two diseases.

Cardiac Lesions Associated with Rheumatoid Arthritis

Opinions as to the presence and nature of cardiac lesions associated with rheumatoid arthritis have varied (Bennett, 1943). According to the older clinical reports, the incidence of cardiac lesions varied from 4 (Coates, 1931; Monroc, 1936) to 40 per cent (Kahlmeter, 1934). The value of these clinical reports is limited because: (1) The type of chronic arthritis studied is not always clearly defined; (2) clinical data are often insufficient so that accurate diagnosis of the nature or site of a cardiac lesion cannot be made; and (3) mild or healed cardiac lesions may give no clinical indication whatsoever of their presence.

Studies of the pathologic changes in the heart, in cases in which chronic infectious arthritis is known to have occurred during the life of the patient, were made by Charcot (1881), Kast (1901) and Grzimek (1932). These studies, however, are difficult to interpret because the type of arthritis is not clearly defined. Baggenstoss and Rosenberg (1941, 1943, 1944) and Rosenberg and asso-



Figure IX-31. Rheumatoid aortic valvulitis. X 8.

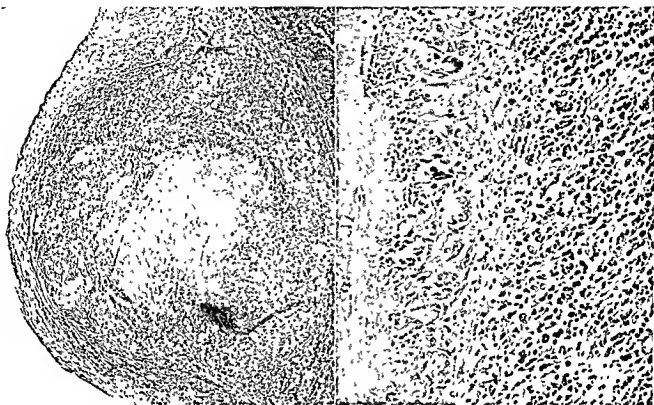


Figure IX-32 Rheumatic aortic valvulitis. Higher magnifications of lesion seen in Figure IX-31 a (left), X 32, b (right), X 195.

ciates (1944) have reported the results of studies at the Mayo Clinic in which both the criteria used for the diagnosis of rheumatoid arthritis and the character of the cardiac lesions were carefully described. Cardiac lesions indistinguishable from those produced by rheumatic fever were found at necropsy in 16 (53 per cent) of 30 cases.

Since these reports were published, 16 additional cases have been studied at necropsy at the Mayo Clinic (Goehrs *et al.*, 1958). Definite pathologic evidence of previous rheumatic injury was present in 16 of the total of 36 cases studied (44 per cent). The pathologic studies of Baggenstoss and Rosenberg have been confirmed by Bayles (1943), Fingerman and Andrus (1943), Smyth (1943), Young and Schwedel (1944), in these reports the incidence of rheumatic heart disease in cases of rheumatoid arthritis varied from 26 per cent (Bayles) to 65.7 per cent (Young and Schwedel). Clinical studies that support the possibility that rheumatoid arthritis and rheumatic fever are related and that rheumatic heart disease is commonly present in rheumatoid arthritis, even in the absence of a history of frank attacks of rheumatic fever were reported by Dawson (1943); Ellman (1944); Feiring (1945);

Coss and Boots (1946); Pickard (1947), and Fischmann and Gwynne (1948). Valaitis and associates (1957) reported an unusual type of aortitis with aortic valvular deficiency in a patient who also had rheumatoid spondylitis. There were several small aneurysmal out-pouchings of the aorta with marked wrinkling of the intimal lining. The aortic cusps were inverted and thickened. Microscopically, necrosis of tissue was predominant with fragmentation of elastic fibers and perivascular lymphocytic infiltrations. While the gross and microscopic findings suggested syphilis, the authors believe that the incomplete type of necrosis of the aortic wall and the focal fragmentation of the elastic tissue of the aorta distinguishes this lesion from that of syphilitic aortitis.

Three possible explanations have been considered for the unexpected high incidence of rheumatic heart disease in cases of rheumatoid arthritis. The first was that, by chance, a series of cases had been studied in which an independent rheumatic heart disease was unusually common. If this explanation is correct, the findings in these cases actually do not reflect accurately the true incidence of the two conditions in the same cases. Statistical studies by Berkson (1940) and Mainland (1953) lend considerable support to this point of view. A second possible explana-

tion was that rheumatoid arthritis and rheumatic fever are related and that rheumatic heart disease is commonly present in rheumatoid arthritis, even in the absence of a history of frank attacks of rheumatic fever. The third possibility considered was that the "rheumatic" cardiac lesions were not caused by rheumatic fever, but represented a similar disease caused by the agent responsible for rheumatoid arthritis. If this is correct, a heretofore unrecognized condition, rheumatoid heart disease, was observed.

It is interesting in this connection that Baggenstoss and Rosenberg (1941; 1944) observed 2 cases in which the cardiac lesions (Figures IX-31 and IX-32a, b) were strikingly similar to the subcutaneous nodules of rheumatoid arthritis. They differed from typical rheumatic lesions in that they were much larger and there was much more necrosis in the central portion.

Similar lesions have since been described by others (Clark and Bauer, 1948, Gruenwald, 1948; Raven *et al.*, 1948, Craf *et al.*, 1949,

Bywaters, 1950; Sokoloff, 1953; Bevans *et al.*, 1954; and Sinclair and Cruickshank, 1956). Schilder and associates (1956) and Clark and co-workers (1957) described cases of rheumatoid aortitis with aortic regurgitation associated with rheumatoid spondylitis. In the latter report, the lesion mimicked syphilitic heart disease but the authors believe it represented a systemic manifestation of rheumatoid disease.

In a review of the necropsies of 36 patients with rheumatoid arthritis at the Mayo Clinic (Coehrs *et al.*, 1958), pathologic evidence of a specific rheumatoid granulomatous type of injury was found in 7. The lesions were located at the base of the mitral and aortic valves, the wall of the left ventricle, the left atrial wall, and the epicardium.

From these reports it is apparent that, in addition to the lesions which cannot be distinguished from those of rheumatic fever, a new type of heart disease has evolved which is apparently specific for rheumatoid arthritis and may be designated as "rheumatoid carditis."

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Nonrheumatic Inflammatory Diseases of the Heart

A. Pericarditis

OTTO SARIM

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A NORMAL PERICARDIUM, like other normal serous membranes, is smooth, glistening and transparent. It is glistening because it is covered by a single layer of mesothelial cells; smooth because the cells are similar over the entire pericardium and are not covered by any foreign material, transparent because there is no other substance between the mesothelium and the underlying subepicardial fatty tissue and myocardium. Any deviation from these three characteristics must be regarded as abnormal. In acute inflammation, the epicardium is covered with fibrin and appears dull because of the presence of exudate over the mesothelial cells; rough because of the irregular distribution of the exudate; and opaque because the underlying tissue is not visible. If the fibrin deposits are recent, they can be scraped away easily and the pericardium will again appear smooth, glistening and transparent. If the epicardium is smooth and glistening but opaque, so that the underlying subepicardial fatty tissue cannot be viewed, there is newly formed connective tissue between the epicardium and myocardium. Such newly formed connective tissue indicates, most com-

monly, scar tissue and one is thus justified in making a diagnosis of healed (circumscribed) pericarditis.

Fluid in Pericardial Sac

Kaufmann (1922) stated that the amount of clear yellow fluid normally present in the pericardial sac is from 5 to 20 ml., and Hall (1918), 5 to 30 ml. According to Karsner (1935), the sac contains about 20 to 50 ml. of fluid. In my experience, the figures that Karsner gives seem more appropriate. An excessive amount of fluid indicates either a transudate or an exudate. Larger amounts of fibrin are always characteristic of an exudate while transudates contain a small amount of fibrin.

Hydropericardium (hydrops pericardii) is most often a sequela of generalized chronic passive hyperemia and may be part of general anasarca. When the fluid is excessive, it may actually compress the veins which open into the atria. In such an event, the arterial pressure is decreased and the venous pressure is increased. The systemic pressure may be sustained for a considerable period of time by vasoconstriction. Increased intrapericar-

dial pressure may affect the heart muscle and its rhythm as a result of relative anoxemia of the myocardium. Alteration of the normal variations of intrapericardial pressure, from accumulation of excessive pericardial fluid, may cause *pulsus paradoxus*. Sometimes, in old people, hydropericardium is the only manifestation of chronic passive hyperemia of serous cavities. Since, in such instances, the heart often is atrophic, the older pathologists coined the term *hydrops ex vacuo*. Large quantities of pericardial fluid, measuring up to 1 to 2 liters, may cause astonishingly little disturbance (Hall, 1948). If, however, the pericardium is thickened as a result of previous inflammation, small quantities of fluid may produce tamponade. The rapidity of accumulation of fluid in the pericardial sac is also important; rapid accumulation of relatively small amounts of fluid (hemorrhage) often causes death, owing to tamponade of the heart, while large amounts of fluid that have accumulated slowly may be well tolerated. An excessive amount of pericardial fluid is often found in *myxedema*. Schnitzer and Gutmann (1946) stated that the similarity of the electrocardiograms in cases of pericardial effusion and in cases of *myxedema* suggest a common abnormality, which may be the presence of excessive fluid in both of these disorders. They remarked that this finding would support the opinion that a pericardial effusion exists in many, if not in all, cases of "myxedema heart."

Hemopericardium. The presence of blood in the pericardial sac may be the result of a penetrating wound of the heart, rupture of an aneurysm of the ascending aorta or of the arch of the aorta, rupture of a recent myocardial infarct, or of a mycotic erosive myocardial aneurysm (see page 715). A hemorrhagic exudate may be the result of infection such as tuberculosis or anthrax, of a primary or metastatic tumor, or of a disease having a hemorrhagic tendency.

Pneumopericardium is a rare condition. It may be the result of perforating trauma, of perforation of a carcinoma of the esophagus or bronchus into the pericardium, or it may occur as a complication of a pyopneumo-

thorax. Rarely gas-forming organisms may produce pneumopericardium, and the term *pneumatosis pericardii* may then be used.

Milk Spots

The most common abnormalities of the pericardium are the so-called pericardial *milk spots*. Other terms are "soldier's spots," "tendinous patches" and "maculae tendineae." They were described as early as 1806 and since that time their origin has been disputed (Nelson, 1940). The old explanation for these spots was mechanical trauma. It was thought that pressure of the sternum upon the ventral wall of the right ventricle, where these patches are most commonly located, produced chronic irritation and resultant chronic inflammation, with new formation of connective tissue between the epicardium and myocardium. It was also thought that the straps of knapsacks carried by soldiers produced such chronic irritation upon the visceral pericardium; hence, such patches were called "soldier's spots." Multiple patches are somewhat more frequent than single ones. Most commonly they are from 1 to 3 cm. in greatest diameter. The right side of the heart is much more commonly involved than the left side.

Nelson, who studied 494 hearts of patients one year old and over, found 170 (34.4 per cent) with one or more pericardial milk spots. Of 439 persons 18 years old and over, the hearts of 165 (37.6 per cent) had such milk spots. Nelson concluded that there should be a definite and marked increase of incidence with age, if the production of milk spots were on a purely mechanical or age basis. However, he could not demonstrate such an increase.

Microscopically, milk spots are characterized by new formation of connective tissue which is covered by normal-appearing mesothelial cells. The connective tissue is loose, and often collections of lymphoid cells are observed. Occasionally, small foci of mesothelial cells, forming pseudo-glandular or canalicular formations, are noted within the loose connective tissue.

It seems evident that these milk spots are the result of old circumscribed pericarditis.



Figure X-1. Uremic pericarditis. Fibrinous exudate. (WCGH, 46 P 14.)

Nelso noted their association with chronic or recurrent valvular heart disease. In his series, the size and the number of milk spots were often increased in patients who had severe coronary atherosclerosis and enlarged hearts. In 20 per cent of hearts that had milk spots, Nelson noted transitions from an active inflammatory process to the usual type of fibrosis.

Acute Pericarditis

The gross picture of acute serofibrinous pericarditis is characteristic. Early lesions are particularly well seen on the visceral pericardium (epicardium). The epicardium loses its gloss and has a deposit of fibrin, giving it a fine granular appearance. In this stage the pericardium looks like velvet. Sometimes, when inspected with a magnifying glass, the fibrin is seen in the form of a minute network which may be scraped away easily with a scalpel. Such early fibrinous pericarditis is often noted in the region of the pericardium covering the great vessels and is probably

in this region of reduplication of the pericardium. Later, when more fibrin is deposited, the netlike arrangement of the fibrin is no longer recognized. The fibrin becomes arranged in small and large nodular clumps and is distributed throughout the parietal and visceral pericardium. Still later, the fibrin appears in the form of characteristic villi, in more or less isolated masses, while the remainder of the pericardium may be more diffusely covered with fibrin. This is the so-called "bread and butter exudate" or the *cor villosum*, the latter term indicating the resemblance to sheep's fur. In addition to the deposit of fibrin, some pus is usually present. If the amount of fluid is minimal, the term *pericarditis sicca* is used. Also, if initially both fibrin and serum are present, the serum alone may be absorbed and thus *pericarditis sicca* may result. Thomas and associates (1953) found a "dry" exudate (*pericarditis sicca*) 8 times among 38 cases of rheumatic pericarditis. According to Ribbert (1897), Mönckeberg explained the formation of villi as follows:

During diastole the epicardium is well expanded but during systole it becomes relaxed and wrinkled. When fibrin is formed, it is deposited principally within the base of the wrinkles; thereafter, additional fibrin becomes adherent to older fibrin and thus the so-called villi are formed.

Microscopically, acute pericarditis is similar to inflammation of other serous membranes. The pericardium is covered by fibrin with many enmeshed polymorphonuclear leukocytes, a few lymphocytes and occasional histiocytes. The subepicardial layer contains dilated capillaries. Some lining mesothelial cells may become desquamated, whereas others are swollen or show fatty degeneration. In purulent pericarditis, polymorphonuclear leukocytes are abundant and many of them show degenerative changes. In severe pericarditis the superficial layers of the myocardium also are often involved.

In *uremic pericarditis* most of the exudate consists principally of fibrin (Figure X-1). Only a few polymorphonuclear leukocytes are

Often, acute fibrinous pericarditis may heal with complete restitution. The lining mesothelial cells regenerate and the inflammatory exudate is absorbed. At other times the acute inflammatory exudate becomes organized and is eventually replaced by granulation tissue and scar tissue. Such scars may be confined to one of the layers of the pericardium. Since they are completely covered by regenerated mesothelial cells, they appear smooth and glistening but opaque. If fibrin extends from the visceral to the parietal layer of the pericardium, newly-formed blood vessels and eventually young fibroblasts and connective tissue fibers will extend from one layer of the pericardium through the fibrin masses to the opposite layer. Thus, organization of fibrin is essential for the production of adhesions between the visceral and parietal pericardium. Gradually granulation tissue, extending from both the visceral and parietal pericardium, traverses the exudate. The entire pericardial cavity may become completely obliterated by adhesions to produce an *adhesive pericarditis with obliteration of the pericardial cavity*. The term *synechia cordis* is also sometimes used to indicate adhesions between the two layers of the pericardium.

The behavior of the lining mesothelial cells in healed or adhesive pericarditis is interesting. It often happens that regeneration of these cells occurs at the base of the normal epicardial wrinkles. When, because of the organization of the exudate, the wrinkles or crevices are bridged over by connective tissue, regenerated mesothelial cells also grow on the inner surfaces of these connective tissue bridges and line the spaces thus created. On microscopic section, therefore, many thin spaces lined by mesothelial cells may be found within the scar tissue close to the pericardial surface (Ribbert, 1897). Since these lining mesothelial cells are often somewhat swollen, the spaces resemble glandular or adenomatous structures (Figure X-2) and occasionally may give rise to droplike cysts covering the pericardium (Lauche, 1919).

In healing of acute pericarditis, when the inflammation also involves the external sur-

faces of the parietal pericardium (external pericarditis), adhesions may involve the mediastinum and adjacent pleura, lungs and intercostal muscles. The term *mediastinopericarditis* is used in such cases

Incidence of Pericarditis

Wells (1902) found pericarditis in 128 of 1048 autopsies; 57 were classified as acute and 71 as chronic. Loeke (1916) found acute pericarditis 150 times and chronic pericarditis 209 times among 3683 autopsies; 88 had milk spots. Among 118 instances of acute pericarditis, 42 were classified as fibrinous, 33, serofibrinous; 4, hemorrhagic, and 39, purulent. Musser and Herrmann (1926) found either acute or chronic pericarditis in 11.9 per cent of 1720 autopsies. Smith and Willius (1932) reported pericarditis in 373 of 8912 autopsies, 144 were classified as adherent pericarditis. These authors also commented upon a distinct predominance of males in the statistics of acute pericarditis.

Causes of Pericarditis

Pericarditis is usually the result of invasion of the pericardium by bacteria. Exceptions to this general rule are met in rheumatic fever, myocardial infarcts, kidney lesions (uremic pericarditis), and tumors (Figure X-7). Bacteria may enter the pericardium as a result of a perforating trauma and of inflammations of neighboring organs or struc-



Figure X-2. Organized pericarditis. Note pseudo-glandular spaces lined by mesothelium. Hematoxylin and eosin. X 150



Figure X-3. Early fibrinopurulent pericarditis secondary to empyema of pleural cavity. From a man of 46. (WCGH, 44 A 412.)

tures. In such cases it is not always necessary to demonstrate the actual extension of the inflammation from the pleura (Figures X-3 and 4), lymph node or anterior mediastinum into the pericardium, since bacteria may find their way to the pericardium by lymphatic spread or "migration," as in instances of peritonitis (Wile and Saphir, 1932). Pericarditis is not a rare complication of myocarditis. On the other hand, pericarditis may also lead to myocarditis. Only rarely may one demonstrate actual extension into the pericardial sac of an abscess of a lymph node, or of a myocardial or pulmonary abscess, or of a pleural empyema.

Zodikoff (1947) recorded an instance of multiple abscesses in the liver with rupture into the pericardial sac. Smith and Willis (1932) pointed out that pericarditis, in their series of 373 cases,

was associated with the following conditions, in the order given: (1) rheumatic fever, (2) intrathoracic infection, (3) cardiac infarction, (4) syphilis (its etiologic role, however, was doubtful), and (5) neoplastic invasion. Egelius and associates (1955) found pericarditis 7 times among 13 cases of rheumatoid arthritis.

It is sometimes difficult or impossible, clinically, to determine the cause of chronic pericarditis. The importance of exact diagnosis has become evident with the development and increased use of chemotherapeutic and antibiotic agents. Pericardial biopsy, as a diagnostic procedure, permits actual direct examination of the pericardial tissue. However, in 5 of 16 patients with pericarditis studied by Proudfit and Effler (1956), the etiology still remained unknown in spite of this procedure.

Pericarditis associated with rheumatic fever, acute bacterial endocarditis, subacute bacterial endocarditis, and myocardial infarction will be discussed elsewhere.

Pericarditis occurs as a complication of pyemias. In such instances, the question is often raised whether the pericardium becomes infected directly by bacteria circulating in the blood stream (*primary pericarditis*) or whether the organisms produce a small abscess adjacent to the pericardium, with perforation of the abscess and resulting *secondary pericarditis*. From studies of the etiology of tuberculous meningitis (Rich and McCordock, 1933) and from personal experience, the latter mechanism seems much more likely. Careful gross and microscopic studies

will almost always disclose a small or minute abscess, most commonly located within the adjacent myocardium or other adjacent structures, with secondary pericarditis. (See also Wile and Saphir [1932] for their discussion of so-called primary peritonitis.) Perhaps an exception to this general rule is the acute pericarditis found in acute rheumatic and similar infections, however, since the myocardium is so often involved in rheumatic disease, the pericarditis may represent an extension of the myocarditis. Among 113 cases of pericarditis with effusion (Smith and Willius, 1932), only 3 were non-inflammatory and 3 were of tuberculous origin; the remainder were classified as acute purulent and acute fibrinous pericarditis with effusion. Most

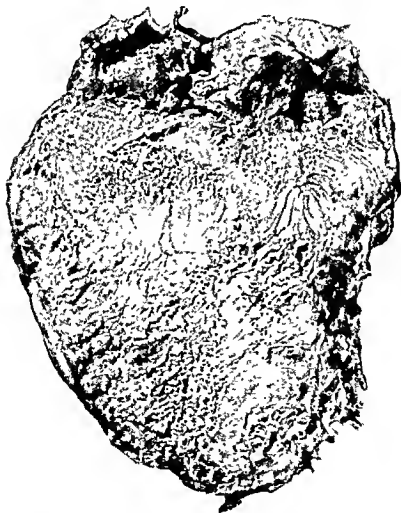


Figure X-4. Organizing acute fibrinopurulent pericarditis secondary to empyema of pleural cavity. Pericardial cavity contained approximately 1000 ml. of fluid. From a man of 70. (WCGH, 40 A 132.)



Figure X-5. Tuberculous pericarditis From a 66-year-old man. (WCGH, 45 A 265.)

often, the pericarditis was associated with an intrathoracic infectious disease. These authors felt that the presence of infectious intrathoracic disease favored the involvement of the pericardium, and that, in infectious processes of the body as a whole, the chances of development of pericarditis are even greater. Thus, the presence of infection should always focus attention on the pericardium, so that purulent pericarditis (Figures X-3 and 4) or fibrinous pericarditis with effusion may be recognized more commonly. In myocardial infarcts, if the necrosis is close to the pericardium, serofibrinous pericarditis may result. This occurs especially in full-thickness infarcts. The ensuing pericarditis is interpreted as an example of a "sterile" inflammation, the necrotic muscle fibers causing a non-specific reaction, not only of the surrounding interstitial tissue, but also of the pericardium. Inasmuch as numerous polymorphonuclear leukocytes surround and infiltrate infarcted muscle fibers, usually large numbers of poly-

morphonuclear leukocytes are also present in such a pericarditis. It is noteworthy that such a pericarditis is not necessarily confined to the portion of the pericardium adjacent to the infarct, but may be diffuse.

Any pathogenic microorganism may on occasion cause acute pericarditis, but staphylococci, streptococci, and *Pseudomonas aeruginosa* are commonly found. *Pasteurella tularensis* (Meredith, 1950) is a rare cause. Hensler (1955) studied 2 instances in which *Haemophilus influenzae* was the causative organism. Infections with amebae and various fungi have likewise been reported. Any organism capable of causing endocarditis or myocarditis may also be responsible for pericarditis (see page 719).

Uremic pericarditis, usually classified as chemical pericarditis, is characterized by the rarity of polymorphonuclear leukocytes. The mechanism of its production is not known. Waeker and Merrill (1954) stated that uremic pericarditis occurs in about 18 per cent

of patients with acute renal failure, and in 51 per cent of those who die with chronic renal failure.

Pericarditis of unknown origin has been called "acute nonspecific pericarditis," "benign pericarditis of unknown origin," and "idiopathic pericarditis." Often a virus has been postulated as the cause. Many such cases have been reported in young adults. The prognosis is usually good.

Davies (1952) has given a short review of the literature and discussed the x-ray and electrocardiographic findings in 5 cases. Fatal cases were reported by Pomerance and associates (1952) and McCord and Taguchi (1951), but Carmichael and co-workers (1951) stressed that long-term follow-up usually indicates a good prognosis. Rabiner and associates (1954) traced only 1 instance of chronic constrictive pericarditis to the acute benign form. Because of certain similarities with rare cases of pericarditis associated with infectious mononucleosis (Miller *et al.*, 1953, Shugoll, 1957; Gerbaut *et al.*, 1958), epidemic parotitis (Magida, 1951), and certain respiratory infections commonly regarded as viral

in origin (Rosenow and Cross, 1951), and because all cultures remain sterile, it is usually believed that these pericardial infections are likewise of viral origin. Cross and Charles (1953) concluded that, because of the frequent association of pericarditis and certain respiratory infections, the pericarditis may be caused by a virus.

Tuberculous Pericarditis. In disseminated miliary tuberculosis, tubercles may be found in the pericardium. Karsner (1955) has pointed out that, while the pericardium that is the seat of miliary tubercles often has little or no inflammation, in tuberculous pericarditis the inflammation is marked, whether it is acute or chronic. At autopsy the pericarditis is usually chronic, with extensive adhesions of both layers of the pericardium, remnants of fibrin and much caseation (Figure X-5). Conglomerate tubercles (Figure X-6) also are often present. The exudate is usually fibrinous in type, with varying amounts of hemorrhage.

Harvey and Whitehill (1937) studied 95 instances of tuberculosis of the pericardium. Peri-

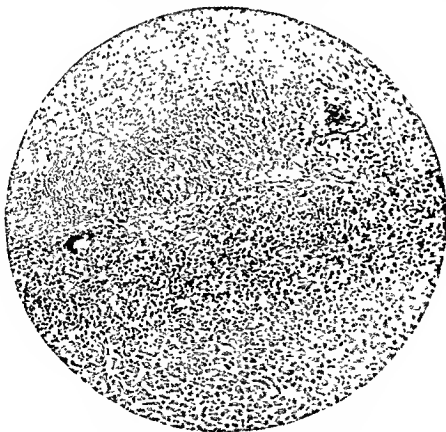


Figure X-6. Tuberculous pericarditis. From same case as Figure X-5. Hematoxylin and eosin. X 265.



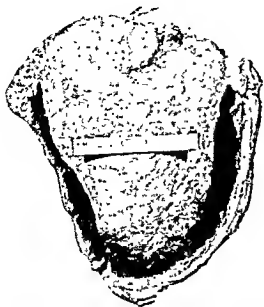


Figure X-7. Fibrinosanguineous pericardial exudate in myelogenous leukemia. From a 9-year-old boy. (WCGH, 57 A 276.)

cardial fluid was examined during life in 13. In 2 of these cases, acid-fast bacilli were found in smears of the sediment, and in 1 case, the organism was cultured; in 5 cases, tubercle bacilli were proved to be present by guinea pig inoculation. In 7 of the 13 cases, therefore, the diagnosis was supported by smear or proved after guinea pig inoculation. In 12 instances a considerable amount of fluid was present within the pericardial sac. The fluid was usually blood-tinged and varied in quantity from 150 to 1350 ml. The pericardial cavity was always enlarged.

In most instances of tuberculous pericarditis, the parietal pericardium is thickened and leathery, and often nodular tubercles are visible from without. Thick, fibrous, organizing adhesions are sometimes noted with adhesions of the pericardium to lungs, diaphragm and sternum. The visceral layer is usually covered by a mass of thick, shaggy, flaky, red fibrin, often assuming a corrugated appearance. Below the superficial layer of fibrin, there is a zone of granulation tissue. On section, many circumscribed, minute, yellow, opaque areas are scattered throughout. Sometimes tuberculous lymph nodes are present adjacent to the pericardium. Most frequently the peribronchial peritracheal and mediastinal nodes are involved and, less com-

monly, the periaortic and anterior mediastinal nodes. Often the pericardial sac is obliterated by fibrous tissue, and yellow areas or nodules with necrotic centers or plaques of calcification may be seen.

In one instance Harvey and Whitehill (1937) thought that the tuberculous pericarditis was primary, since at autopsy the mediastinal nodes were normal, the lungs showed no abnormalities, and no other tuberculous lesions were found. Among 136 autopsies performed on children with various forms of tuberculosis, tuberculous pericarditis was found 8 times by Boyd (1953). Baird and Walsh (1954) stated that the incidence of tuberculous pericarditis among all patients coming to autopsy was 1 per cent.

In a study by Myers and Hamburger (1952), of 9 patients with clinical tuberculous pericarditis not treated with streptomycin, 5 died within a period of a few months, from miliary spread of tuberculosis or from cardiac failure. Spontaneous healing of the pericarditis occurred in the other 4, but tuberculous foci subsequently appeared elsewhere in the body. Three other patients treated with streptomycin recovered. A pericardiocentesis and the demonstration of tubercle bacilli in the removed fluid aided in the clinical diagnosis of some of these patients.

Syphilis of the Pericardium. *Gummata* of the pericardium have been reported in the older literature (see Mönckeberg, 1924). They are extremely rare. The occurrence of syphilitic pericarditis is questionable. Stockmann (1904), who collected from the literature 79 instances of gumina of the myocardium, found that 10 of these hearts also had pericardial lesions. Six of the 10 showed either complete or partial adhesions of both layers of the pericardium.

Other Infections. Cornell and Shookhoff (1944) collected 65 instances of *actinomycosis* of the heart and mentioned involvement of the pericardium. *Amebic pericarditis* had been described 22 times, according to Kern (1945), though pericardial involvement in the course of amebic abscesses of the liver has been reported more frequently. Kern studied an instance of amebic pericarditis subsequent to extension of an amebic abscess of the liver. *Endamoeba histolytica* was demonstrated in the pericardium. The clinical impression had been tuberculous pericarditis.

D'Mello (1947) reported perforation into the pericardial sac of a large amebic abscess of the liver, with the production of pericarditis and the finding of amebæ in the pericardial cavity. (See page 824.)

We have observed an instance of a *geothrix* infection of the pericardium and myocardium. The portal of entrance was apparently the region of the pharynx. The patient had been admitted to the hospital for treatment of a reticulum cell sarcoma. When he developed acute pharyngitis with fever, large amounts of penicillin were administered. He died 10 days later from a pulmonary and systemic fungus infection which involved the myocardium and pericardium.

Adherent Pericardium. Adhesions between the parietal and visceral layers of the pericardium may represent either chronic pericarditis or the end-stage of acute pericarditis. The chronicity of the inflammation must be proved microscopically, i.e., there must be evidence that active inflammation is still present and has not come to a standstill. True chronic adhesive pericarditis is common in rheumatic fever and in tuberculosis. As a result of adhesions between the two layers of the pericardial sac, the pericardial cavity may be partially or completely obliterated (*synechia cordis*). The older pathologists spoke of "concretio cordis." The connective tissue forming these adhesions often becomes hyalinized and sometimes calcified, particularly in old tuberculous pericarditis. Well-marked calcification of portions of the pericardium occurred in 15 of the 144 cases of adherent pericarditis reported by Smith and Wallius (1932) and in 4 of Wells' (1902) series. Wells pointed out that *synechia cordis* may be present without any effect upon the patient.

Mediastinopericarditis refers to the condition in which fibrous tissue binds the heart firmly to the adjacent tissues, including the rigid structures, ribs and their cartilages, sternum and vertebral column. In the older literature, this was called *accretio cordis*. The firm attachments of the heart to the neighboring structures frequently result in retraction of the precordial interspaces with each contraction of the heart. This is regarded by most observers as an added burden on the

heart, and it may be a factor in the cardiac enlargement and heart failure which occur not infrequently in these patients. Laws and Levine (1933) found that the average weight of the heart in patients with mediastinopericarditis and valvular disease (654 grams) was greater than the weight of the heart in patients with valvular disease only (534 grams). This may indicate that external adhesions increase the work of the heart. However, many investigators doubt that hypertrophy is the direct result of overwork of the heart because of adhesions. Hypertrophy is often encountered in such hearts and is explained on the basis of valvular lesions which also are often present. It must be pointed out that it is extremely difficult to determine the weight of the heart in instances of old pericarditis with adhesions (constrictive pericarditis and mediastinopericarditis). The weights usually given represent the combined weight of the heart and the adhesions, and it is difficult to judge the degree of hypertrophy. Usually, when old valvular diseases are found, the hypertrophy of the heart is believed to be the result of these valvular changes. Thus, in a case of Mallory (1917), the heart and the pericardium together weighed 450 grams but the heart was actually small, its weight being estimated to be about 250 or 275 grams. Mediastinopericarditis may be caused by rheumatic fever or by tuberculosis, or may be a complication of purulent pericarditis.

Constrictive pericarditis. Sometimes, as the result of healing of purulent or tuberculous pericarditis, dense and thick adhesions are formed, and layers of the pericardium may become rigid and actually cause limitation of the diastolic expansion of the heart (Wells, 1902). This condition is termed *constrictive pericarditis*. The outstanding physiologic effect in such patients is the reduced inflow of blood to the heart. This is recognized clinically by dyspnea on exertion, cyanosis, ascites, increased venous pressure, and low pulse pressure. Blalock and Burwell (1941) defined chronic constrictive pericarditis as a thickening and contraction of the pericardium or epicardium, or both, to the extent of interference with the normal action of the

heart. The pericardial sac may be completely obliterated or may have areas in which the two layers are not adherent. The pericardium may or may not exhibit areas of calcification; usually it does not. Small collections of fluid may be trapped between the thickened epicardium and pericardium. Associated disease of the heart itself is rare, except for atrophy of the myocardium in advanced cases. In a number of reports, this condition was recognized clinically and operation was performed to cut the adhesions (Beck, 1931, Blalock and Burwell, 1941). From the foregoing, it is evident that mediastinopericarditis occasionally may lead to some obstruction of flow of blood to the heart, particularly if the region of entrance of the inferior vena cava into the right atrium is involved. This type of mediastinopericarditis is also referred to as constrictive pericarditis.

It is sometimes stated that constrictive pericarditis is caused by rheumatic fever.

However, Harrison and White (1942) are certain that rheumatic fever is rarely, if ever, an etiologic factor. It is apparently much more often caused by tuberculosis.

Pick, as early as 1896, concluded that a complex of symptoms similar to that produced by primary cirrhosis of the liver could be caused by an old but clinically latent fibrous pericarditis. As a result of the pericarditis, circulatory disturbances of the liver ensue, with stasis in the portal circulation and proliferation of connective tissue within the liver, and finally severe ascites. He used the term "pericarditic pseudocirrhosis of the liver." He also emphasized that the syndrome of Curschmann, characterized by severe ascites and perihepatitis, was the result of an old pericarditis. Curschmann (1884) had stated that primary perihepatitis (frosted liver, hyalocapsulitis) may be so severe as to cause encroachment upon the liver parenchyma and the branches of the portal vein by the newly-formed contracting connective tissue and thus produce severe ascites. However, Pick pointed out a few years later that Curschmann's patient also had an old pericarditis. Pick, therefore, thought that the ascites and perihepatitis were the result of the old pericarditis. Eisenmenger (1900) admitted that severe ascites may occur in adhesive pericarditis in the absence of edema of the lower extremities. He thought that the ascites was not the result of vascular distur-

ances within the liver itself, with consequent fibrosis, but that it was caused by several factors, primarily compression or angulation of the inferior vena cava or perhaps localized peritonitis at the hilus of the liver. Therefore, he condemned the term "pericarditic pseudocirrhosis of the liver," because this terminology would embrace only a single etiologic factor. Monckeberg (1924) advocated the term "Pick's disease" for those instances in which adhesive pericarditis, adhesive pleuritis and hyalocapsulitis (Zuckerguss, cake-icing) of the liver, are present. It is imperative in such instances to examine carefully the inferior vena cava at its entrance into the right atrium. Because of mediastinopericarditis, this portion of the inferior vena cava may become narrowed and lead to severe distention of the hepatic veins and ascites. Monckeberg also described a type of old pericarditis without adhesions, but with marked fibrosis of both layers of the pericardium, also with nodules consisting of completely organized fibrin covered by mesothelium. Both layers of the pericardium may then have thick, white, smooth or nodular surfaces, and the term "frosted" pericardium (Zuckerguss-herz) may be applied. Kaufmann (1922) pointed out that such a "frosted" pericardium in particular may give rise to Pick's syndrome with hyalocapsulitis of liver and spleen (Zuckergussleber and Zuckergussmilz). White (1931) stated that Pick's disease may or may not be associated with polyserositis (Concato's disease).

Occasionally, as a result of an adhesive pericarditis, granulation tissue and resulting scar tissue cause narrowing of the inferior vena cava at the site of its entrance into the right atrium. This constriction is situated just above the opening of the hepatic veins into the vena cava. Apparently, because of the angle formed by the vena cava and the hepatic veins, there is a damming back of blood into the liver. The circulation of the vena cava below this level is relatively not impeded. The openings of the hepatic veins into the inferior vena cava, however, are greatly dilated and, as a result, the liver develops a diffuse periportal fibrosis but not a true cirrhosis. Ascites then appears but is not accompanied by edema of the lower extremities. In a patient observed by us, the ascites was early and persistent, but there was no edema of the lower extremities. It is evident that these changes will be much more severe if complicated by old endocarditis of the tricuspid valve, since insufficiency of this valve increases the resistance of inflow into the right

atrium. This type of pericarditis is really a mediastinopericarditis.

Pericarditis with much cholesterol within the inflammatory exudate was described first by Daniel and Puder (1932), and later by Mernill (1938). It was suggested by the former authors that the cholesterol was a secondary deposit in certain instances of tuberculous pericarditis with hemorrhage into the pericardial sac. From the description, however, it seems possible to explain the presence of cholesterol as a result of a coincidental fat necrosis occurring within the subepicardial fat tissue. Creech and associates (1955) reported the association of "cholesterol pericarditis" with myxedema.

Calcification of the Pericardium is occasionally seen as the end result of an old pericarditis. It is found relatively often in association with tuberculous pericarditis.

Among Smith and Willis' (1932) 144 cases of chronic adherent pericarditis, there were 15 with calcification of the pericardium. In one heart the calcification involved the entire pericardium with the exception of a small portion of the apex. These authors also thought that the single etiologic factor which affected the largest number of patients was rheumatic infection. In Harrison and White's (1942) series, 43 per cent of hearts had calcification of the pericardium. However, as stated before, they believed that rheumatic fever is rarely, if ever, an etiologic factor. Monckeberg (1924) was of the opinion that old masses of fibrin which do not become organized, gradually become calcified. Very rarely the entire pericardium may consist of many masses of calcium. This condition may be found at autopsy in persons who had no cardiac symptoms during life.

Nomenclature. Various terms have been used to describe adhesions between the pericardium and the adjacent structures. By *adhesive pericarditis* is meant adhesions be-

tween the visceral and parietal layers of the pericardium. *Synechia cordis* and *concretio cordis* are older terms. Such adhesions may not produce clinical evidence of disease.

If adhesions are found between the outer portions of the pericardium and adjacent structures, the term *mediastinopericarditis* is applied. The older nomenclature was *accretio cordis*. Mediastinopericarditis may not necessarily cause obstruction of flow of blood to the heart. It is often seen in old rheumatic fever, accompanied by evidence of old endocarditis. The hypertrophy of the heart is often the result of co-existent valvular disturbances. *Constrictive pericarditis* is a form of mediastinopericarditis in which mediastinal adhesions to the pericardium have produced disturbances of inflow of blood. Such disturbances may be caused by constriction in the region of the inferior vena cava just as the latter enters the right atrium and also by constriction elsewhere in the right atrium or in the ventricle. Rarely, rigid (calcified) layers of the pericardium cause limitation of the diastolic expansion of the heart; such a pericarditis is also classified as constrictive pericarditis. Angulation of the inferior vena cava in the region close to the openings of the hepatic veins into the inferior vena cava may be caused by mediastinal adhesions. (Such patients may have severe ascites but no edema of the lower extremities.) Constrictive pericarditis rarely is caused by rheumatic fever and more commonly, by tuberculosis.

In *Pick's disease* there is constrictive pericarditis with angulation of the inferior vena cava close to the opening of the hepatic veins, and associated polyserositis with perihepatitis and perisplenitis.

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B. Endocarditis (Nourheumatic)

OTTO SAPIIR

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PATHOLOGY has cleared the way for clinical medicine in providing an explanation for many clinical signs and symptoms. In this chapter, wherever deemed important, reference is made to clinical medicine and to therapeutic agents. Obviously, in order to have a proper understanding of disease in the patient, one must have a knowledge of the pertinent pathologic changes.

This chapter concerns the various endocardial lesions, with the exception of rheumatic endocarditis which has been treated sep-

arately (Chapter IX). It discusses their incidence, causes, differential morphologic characteristics, associated lesions and complications. The present-day concept of fetal endocarditis and the results of attempts at experimental production of acute and subacute bacterial endocarditis are given. In this discussion the pertinent literature is quoted in an effort to keep the various concepts up to date.

Quotations that are not supported by proof may be challenged in some instances. Even

in this relatively small sphere of pathology there are still a number of unsolved problems. Just what is subacute bacterial endocarditis? Is there an endocarditis caused by toxins? Does endocarditis exist in the absence of verrucae or vegetations? Such questions are presented in the hope of arousing interest and of stimulating research in unsolved problems.

Classification of Endocarditis. Terminology. The term *endocarditis* is usually used to designate inflammation of the valvular endocardium, while *mural* or *parietal* endocarditis denotes inflammation of other portions of the endocardium. The only way in which to recognize acute endocarditis grossly is by the detection of verrucae or vegetations attached to the heart valves and the finding of ulcerations. Whether or not "valvulitis" can be recognized grossly in the absence of verrucae will be discussed subsequently.

Endocarditis is generally classified as acute, subacute, chronic, and recurrent, also as bacterial, nonbacterial, and syphilitic. Anatomically it is designated as verrucous, vegetative and ulcerative. By *verrucae* are meant minute or small wartlike excrescences. Verrucae have been more fully discussed in the chapter on rheumatic endocarditis (Chapter IX). The earliest changes are probably a swelling of the collagen just beneath the endothelium covering the valve with slight or no cellular infiltration. The swollen extruded collagen fuses with the precipitated fibrin and platelets, which together form the verruca. Verrucae vary in diameter from about 1 to 4 mm. By *vegetations* are meant large, septic thrombi.

Sometimes the terms "simplex," "productive" or "rheumatic" are used in the same nonspecific sense as "verrucous;" and the terms "malignant" "ulcerating" or "necrotizing," to denote vegetative and often ulcerating endocarditis (Kaufmann, 1922). Ziegler (1888) used the term *thrombo-endocarditis superficialis* (or *simplex*) for verrucous endocarditis, and *thrombo-endocarditis septica* (or *ulcerosa*) for vegetative or ulcerating endocarditis. Aschoff (1919) also used Ziegler's nomenclature.

Clawson (1924), in an analysis of 220 instances of endocarditis, divided active endocardial lesions into bacterial and rheumatic types.

The former is again divided into acute (primary and secondary) and subacute. The term "primary acute bacterial endocarditis" indicated that no other primary focus of infection existed and "secondary acute bacterial endocarditis," that the endocarditis was associated with another disease, acute or chronic.

Gross and Friedberg (1936) recommended use of the following classification of endocarditis:

- I. Bacterial (bacteria cultivated consistently from blood during life or from vegetations at autopsy)

- A. Acute

- B. Subacute

1. With bacteraemia

2. In bacteria-free stage

- II. Nonbacterial

- A. Rheumatic

- B. Atypical verrucous

- C. Nonbacterial thrombotic

- III. Syphilitic (involving only aortic valve)

The following discussion of acute endocarditis will be based on both the etiologic and anatomic classifications. Most forms of acute verrucous endocarditis are the result of acute rheumatic fever, and their gross and microscopic appearances have been discussed in the chapter on Rheumatic Diseases. Non-rheumatic forms of acute verrucous endocarditis include (1) bacterial endocarditis, (2) so-called endocarditis minima (*marantic* endocarditis), (3) the *indeterminate* form of endocarditis and perhaps (4) certain "toxic" forms of endocarditis. *Bacterial endocarditis* (the term "infective endocarditis" is more generally used in the British literature), which constitutes the largest of these groups, is caused by well-known microorganisms, is characterized by the formation of large vegetations, and often show small or large ulcers and even perforation of the valve. Both acute and subacute bacterial endocarditis fall under this heading. These will be discussed separately with respect to their gross and histologic appearances and their etiology. Sometimes, however, it is not possible to separate

these two types, even after careful study. Some overlapping in this discussion, therefore, is inevitable. Both forms, however, will

be treated together with respect to complications and associated diseases.

BACTERIAL ENDOCARDITIS

Acute Bacterial Endocarditis

Incidence. It is difficult to obtain from the literature data on the incidence of acute bacterial endocarditis. Thus, Ribbert (1924) in his extensive monograph does not state how frequently such lesions are encountered at autopsy in a general hospital. Buday (1929) found 364 instances of various recent and old fatal valvular diseases in a series of 6155 autopsies. Among these were 87 examples of subacute bacterial and 44 of acute bacterial endocarditis. Martin and Adams (1938) reported 157 instances of vegetative endocarditis in a series of 17,000 autopsies. Goldburgh and associates (1942) reported 646 cases of acute bacterial endocarditis in 26,007 autopsies. They found the following valves involved:

Mitral only	308
Aortic only	164
Mitral and aortic	121
Tricuspid only	20
Mitral and tricuspid	10
Aortic, mitral and tricuspid	7
Pulmonic only	5
Aortic and tricuspid	5
Mitral, pulmonic and tricuspid	3
Mitral, aortic, tricuspid and pulmonic	3

Reinhardt (1920) studied 158 cases. He found the valves of the right ventricle only to be involved 15 times; the pulmonic valve, 9 times, the tricuspid valve, 5 times; and both valves, once. In 12 instances, valves of both ventricles were diseased. The aortic valve only was the seat of the disease 50 times; the mitral valve only, 42 times; and both valves, 36 times. Ribbert believed that the aortic valve is the one most often affected. Clawson (1941) found 514 cases of bacterial endocarditis among 30,265 autopsies. In 49 cases with primary acute bacterial endocarditis, death occurred within less than six weeks after the beginning of symptoms. Secondary bacterial endocarditis was found in 101 cases (Table X-1). Among 1000 consecutive autopsies at Michael Reese Hospital, acute bacterial endocarditis was found 17 times. The mitral valve only was involved 12 times; the aortic valve only, once; and both valves, 4 times.

Baum and associates (1958) identified the causative organisms in 19 of 23 cases of bacterial endocarditis predominantly or exclusively involving the right side of the heart. *Staphylococcus aureus* or *Micrococcus pyogenes* was found in 11 cases, *Diplococcus pneumoniae* in 3, *Streptococcus viridans* in 2, *Neisseria gonorrhoeae* in 1, *Streptococcus hemolyticus* in 1 and *Streptococcus fecalis* in 1.

Age and Sex Distribution. Table X-2, taken from Thayer (1931) shows the incidence of acute bacterial endocarditis caused by several organisms, according to distribution by age in decades.

In streptococcal endocarditis, the percentile distribution between the sexes was equal to that of the ordinary hospital representation: men, 111 (56.6 per cent); women, 85 (43.4 per cent); the

TABLE X-1

Age and Sex Incidence in 151 Cases of Primary Acute and Secondary Acute Bacterial Endocarditis (From Clawson, 1941)

Decade	Number of Autopsies	No. of Cases of Primary Acute Endocarditis	No. of Cases of Secondary Acute Endocarditis
Males			
1	2,978	1	1
2	645	3	1
3	1,324	3	6
4	2,052	3	11
5	3,132	8	8
6	3,439	2	10
7	3,350	4	8
8	2,172	1	3
9	565	0	2
10	28	0	0
Totals	19,685	25	50
Females			
1	2,208	2	2
2	574	4	2
3	1,174	5	16
4	1,283	8	14
5	1,347	0	5
6	1,411	1	7
7	1,342	2	4
8	930	2	0
9	279	0	1
10	32	0	0
Totals	10,580	24	51

TABLE X-2

Incidence of Acute Endocarditis, Caused by Several Bactera, According to Age by Decades (Thayer, 1931)

Decade	<i>Streptococcus</i>		<i>Diplococcus pneumoniae</i>		<i>Staph aureus</i>	
	No. Patients	%	No. Patients	%	No. Patients	%
1st	12	6.1	1	3.1	4	12.5
2nd	22	11.2	4	12.5	7	21.8
3rd	55	28.1	22	68.8	6	18.8
4th	47	24.0	3	9.4	6	18.8
5th	26	13.3	1	3.1	2	6.2
6th	24	12.2	1	3.1	6	18.8
7th	10	5.1			1	3.1
All	196	100.	32	100.	32	100.

same was true as to race: white persons, 152 (77.5 per cent), Negroes 44 (22.4 per cent).

Among those with pneumococcal endocarditis, there were more men (71.8 per cent) than women (28.1 per cent), and more Negroes (56.2 per cent) than white persons (43.8 per cent). The incidence of endocarditis caused by *Staphylococcus aureus* was equal in the two sexes. Twenty-two patients (68.7 per cent) were white and 10 (31.3 per cent) were Negro. Table X-1 from Clawson gives the age- and sex-incidence of 49 cases of primary acute endocarditis and 101 cases of secondary acute bacterial endocarditis.

In a review of 700 postmortem examinations of persons 60 years old and over, Zeman and Siegal (1945) encountered 9 instances of acute bacterial endocarditis. Bain and associates (1952), who reported a case of bacterial endocarditis in a 15-month-old infant, remarked on its rarity in children under 2 years of age. They stated that older reports gave the incidence of this disease in children less than 2 years of age as only 0.4 per cent of all cases of bacterial endocarditis.

Gross Appearance. Acute bacterial endocarditis is characterized by vegetations which vary in size and shape. They are usually situated along the line of closure of the valve, but may be present anywhere on the valve and often involve the free margins. Large vegetations are often formed by the confluence of smaller ones. They vary from 4 mm. to 2 cm. in diameter. Their color is yellow-red or yellow-gray. They usually are attached to the valve by a broad base, but the more superficial portions of the vegetations are soft

and break off easily. In such instances, or when necrosis has occurred within the superficial portions of the vegetation, the remaining defect is irregular in contour. At autopsy, often a recent thrombus or clot is found closely attached to this defect. It is thus sometimes difficult to decide which part of the vegetation is the older or true vegetation, and which part is the superimposed clot. The latter has a characteristic currant-jelly color; it often breaks loose if exposed to a stream of water, or it can easily be separated from the vegetation by means of forceps. The superficial portions of the valves involved by vegetations often become necrotic, and when the necrotic material has sloughed away, smaller or larger ulcers are exposed at the free margins of the cusps or leaflets. The adjacent endocardium is red and swollen. It is sometimes difficult to distinguish between an ulcer within the cusp and a defect of an eroding sessile vegetation. The necrotic portion of the valve and the attached vegetation form one unit and may slough together. The adjacent border of the cusp is ragged, irregular in outline, and often the seat of minute ulcers situated at the free margin (Figure X-8).



Figure X-8. Acute bacterial endocarditis with perforation of anterior leaflet of mitral valve. Pneumococcus, Type 25, was recovered from sputum and blood during life, and from lung and valvular vegetation at autopsy. From a patient with unresolved pneumonia. (WCCII, 40 A 198.)

Frank ulcers of various shapes and forms are common. They may be situated at the free margin of the valve, causing a ragged appearance, in the midportion of the valve, surrounded by vegetations, or they may be covered by vegetations. Cecil and associates (1948) reported a perforating ulcer of the aortic valve. The perforation apparently became secondarily covered by recent vegetations which, it was believed, had caused an improvement in the patient's condition.

If the vegetations grow on a valve which previously was normal, the valvular tissue adjacent to the vegetations is usually edematous and red but sometimes grossly normal.

Allen (1939a) stated that it is generally agreed that acute bacterial endocarditis occurs on a previously existing valvular deformity in from 50 to 75 per cent of cases, but this figure seems, from our experience, too high. In Buday's (1929) series of 31 cases of acute bacterial endocarditis, vegetations were found on normal valves 22 times. Whenever evidence of an older valvular lesion is encountered, the possibility of subacute, as opposed to acute, bacterial endocarditis should be considered.

Location. Most commonly the vegetations of the aortic cusps are located on the ventricular aspect and the vegetations of the mitral leaflets on the atrial aspect. However, when the mitral valve is involved by extension of the inflammatory process from the aortic valve, the endocarditis is, of course, located on the ventricular surface of the aortic leaflet of the mitral valve. The vegetations are often not confined to the valves. The infection of the aortic valve may extend to the adjacent aortic intima and produce an acute vegetative endocarditis. A mass of vegetations may involve the cusp, the intima facing the sinus of Valsalva and the intima of the adjacent ascending aorta. The vegetations may extend to the mural endocardium of the adjacent interventricular septum or, more commonly, to the aortic leaflet of the mitral valve. The endocarditis of the mitral valve may extend to the endocardium of the left atrium or may involve the chordae tendineae and also the

papillary muscles. Occasionally the involved chordae may rupture.

Parietal and Contact Endocarditis. Parietal or mural endocarditis may be the result of either direct extension of the valvular endocarditis to the adjacent mural endocardium, or contact of bacteria-laden vegetations with the opposing region of the mural endocardium as the result of the cardiac movements. Such "contact" endocarditis is often encountered on the ventricular aspect of the aortic leaflet of the mitral valve since, in the presence of large vegetations on the aortic valve, this mitral leaflet during diastole is often in contact with the vegetations. The occurrence of isolated mural bacterial endocarditis is rare.

Ribbert (1924) admitted that he had never seen such an instance but referred to rare reports in the older literature. Thus, Schulz (1884) had reported in a patient with puerperal sepsis, a cloudy, more or less circumscribed area of mural endocardium of the left ventricle which was covered with fibrin and soft thrombi, while the valvular endocardium was not involved. (See also page 721.) Small white thickenings of the endocardium are not infrequently encountered. These are sometimes interpreted as healed mural endocarditis; they will be discussed later.

Valvular Aneurysms. Though, strictly speaking, valvular and erosive endocardial and myocardial aneurysms are classified as complications of acute bacterial endocarditis, for convenience they are discussed at this point. Because of the inflammation and subsequent necrosis of portions of the cusp, and the aortic diastolic pressure exerted upon the sinus of Valsalva, the respective aortic cusp may rupture. The intracardiac pressure may lead to rupture of a necrotic portion of a leaflet of the mitral valve. Sometimes the rupture involves only the midportion of a leaflet. This opening may become covered again by vegetations. However, the intraventricular pressure may cause outpouchings of the friable thrombus in the ruptured portions of the valve and lead to formation of false aneurysms. Such false aneurysms occur most frequently on the aortic cusps and less frequently on the aortic leaflet of the mitral valve. Ero-

sive aneurysms may be the result of ulcerations of the leaflet with destruction of the fibrosa (see terminology used by Gross and Kugel, 1931) and extension to the auricularis, leaving the endocardial layer and the auricularis elastic lamellae (leaflet of the mitral) relatively intact. The status of aneurysms is only temporary, for subsequent perforation is bound to occur.

Rubbert (1924), in a detailed discussion, pointed out that it is difficult to distinguish grossly between false aneurysms which result from primary rupture and subsequent attempted closure of the points of rupture by thrombi and erosive aneurysms. This difficulty arises because a thin layer of fibrin may grossly simulate a thinned-out but preserved valvular endocardial layer, and only microscopic examination of the outpouchings may reveal its exact nature. Rubbert coined the term "thromboaneurysm" to denote the origin of these false aneurysms. Kaufmann (1922) made a distinction between acute and chronic valvular aneurysms. The former are the result of ulcerating endocarditis with necrosis of the involved portion of the valve. As for the latter, he merely mentioned that there may be a "chronic outpouching" of the cusps in endocarditis, which may rupture, but he gave no details. Whether those chronic aneurysms are true aneurysms he did not state. It must be noted that true aneurysms of the valves do exist and that they occur in the healing stages of subacute bacterial endocarditis. They will be discussed later.

Erosive Aneurysms. The term "erosive aneurysm" seems preferable to such terms as "embolic" or "mycotic aneurysm." *Embolic aneurysms* are the result of the lodging in blood vessels of hard particles which, because of their density, penetrate into the vascular walls and lead to local dilatations (Karsner, 1955). Infected embolic aneurysms are called *mycotic aneurysms* even though "mycotic" literally has reference to a fungus. Such "mycotic" or "infected embolic" aneurysms are caused by infected emboli which either become adherent to the intima of a blood vessel or lodge in vasa vasorum of larger blood vessels. Infected emboli may also lodge on the endocardium and may cause a mural endocarditis and subsequently an embolic aneurysm, or they may be brought to the heart by

the coronary arteries. However, if there is an extension of an inflammatory process from an acutely diseased valve of the heart to the adjacent endocardium or to the intima of the structures of the sinus of Valsalva with resulting ulcerative mural endocarditis or endarteritis, respectively, and destruction of the myocardium (or media) with consequent local dilatation, the term *erosive aneurysm* is appropriate (Karsner). Since erosive aneurysms are the result of infected vegetations, or of localization of virulent organisms, they are also "mycotic" aneurysms.

Pathogenesis. Erosive aneurysms also involve the aortic intima, the adjacent endocardium and subsequently also the myocardium close to the involved valve. As a result of a mural or parietal endocarditis the involved endocardium and subjacent myocardium may become necrotic. In this event, the necrotic material will be gradually excavated by the impact of the blood stream and eventually will slough, leaving a defect of the mural endocardium and myocardium bordered by inflamed myocardium. The defect constitutes an acute myocardial, mural or so-called *cardiac ulcer*. Such an ulcer in the interventricular septum on the left ventricular aspect may cause bulging of the septum into the right ventricle and thus lead to the formation of an erosive mycotic aneurysm. Similar ulcerations may be present in other locations and lead to bulging into the pericardial sac. Eventually such erosive mycotic aneurysms may rupture. Rupture into the pericardial sac is almost always preceded by acute purulent or organizing pericarditis. As a matter of fact, Ponfiek (1873) has noted that the cardiac wall often behaves like an artery, and the pericardium like the arterial adventitia. Just as the adventitia is thickened over an arterial aneurysm, so is the epicardium thickened by chronic defensive inflammation in the region of the aneurysm. This thickening of the pericardium protects the aneurysm. Rupture of the heart may, therefore, be gradual, with slow leakage of blood into the pericardial sac through one or several small openings, and successive clotting of blood in layers on the surface of the heart.

The presence of old or recent pericardial adhesions frequently prevents a large, immediately fatal extravasation of blood.

Acute purulent pericarditis is the result of either an extension of the inflammatory process, or of migration of organisms to the adjacent epicardium along the lymphatics. Sometimes mycotic aneurysms which involve the endocardium and myocardium may be caused by infected emboli that arise from vegetations and lodge in coronary arterial branches within the myocardium. Commonly, emboli are carried into branches of the coronary arteries with resulting necrosis, minute infarcts or abscess formation. Such an abscess may extend into the mural endocardium which then is covered with thrombi and also undergoes necrosis. The necrotic material in turn will be sloughed, leaving an ulcer which becomes the seat of a mycotic aneurysm. It may then be impossible to determine whether such a mycotic aneurysm was mycotic embolic or mycotic erosive in origin. A mycotic aneurysm of this type may also perforate into the pericardium or, if present within the septum, into the right or left ventricle or into both ventricles.

Perforation of aneurysms. Of 15 instances of perforated embolic and erosive aneurysms of the heart reported by Pirani (1943), 12 were erosive and 3 were embolic. Among 734 instances of cardiac rupture reported by Krumbhaar and Crowell (1925), and by Davenport (1928), abscesses of the heart (probably embolic aneurysms) were encountered only 5 times.

A common site of rupture is the ventral wall of the left ventricle close to the atrioventricular groove. Pirani believed that this predilection is to be explained by the particular structure of the myocardial-aortic juncture and by the presence of abundant subepicardial fat, giving this region less resistance. From this area, the septic process may easily extend to the myocardial tissue near the aortic ring, follow the loose fibrous connective tissue around the large branches of the left coronary artery, and thus reach the pericardium. Rare *dissecting aneurysms* of the heart, following acute bacterial endocarditis, are also

reported. Four cases of Pirani's series were dissecting aneurysms. (See also section on Subacute Bacterial Endocarditis.)

Microscopic Structure of Normal Heart Valves. Before discussing the microscopic picture of acute bacterial endocarditis, it might be profitable to give a short general description of the heart valves, with relevant illustrations (Figure X-9). Both the description and illustrations are taken from Gross and Kugel's study (1931).

The heart valves have certain general features in common and yet sufficient individual differences to distinguish them sharply from each other. All the valves carry as a backbone a dense collagenous layer, for which Gross and Kugel propose the term *fibrosa*. On the atrial aspect of the atrioventricular valves, as well as on the ventricular aspect of the semilunar valves, the *fibrosa* shows a loose structure which they call *spongiosa*. In the semilunar cusps this looser structure may be so conspicuous as to constitute a sharply defined layer. Each valve cusp is attached at its base to a more or less dense connective tissue structure called *annulus fibrosus*. The extent, distribution and connections of the annulus differ considerably with the various cusps. Its topography for the aortic valve has been described by Lewis and Grant (1923). It constitutes an important strategic site which includes part of the base of the valve as well as the adjacent portion of the annulus. Gross and Kugel designate this area as the ring. The rings of the semilunar valves generally contain a conspicuous *spongiosa*, while the atrioventricular valvular rings in this area show only a slightly looser structure of the collagenous *fibrosa*, designated *ring spongiosa*. The *fibrosa*, with its looser layer, is clothed on both sides by a continuation of the arterial intima or ventricular or atrial endocardium, as the case may be. These arterial or endocardial connective tissue mantles contain more or less conspicuous elastic sheets. The elastic sheets which are situated on the outflow surface of the valve (atrial surface of the atrioventricular valves and ventricular surface of the semilunar valves) are generally the heavier and longer. Both elastic layers

thin out progressively as they approach the tip of the valve.

As a generalization, it may be stated that while the separation of these layers of the valves is already seen in early fetal life, they become more and more clearly defined in advancing postnatal life. Furthermore, the differences in their extent, thickness, structure and distribution give to each cusp, its individual characteristics. Figure X-9, taken from Gross and Kugel's article, outlines the more important histologic details of the valves.

Histologic Changes in Acute Bacterial Endocarditis. An excellent description of the pertinent histologic changes is found in Ribbert's monograph (1924). The vegetations of acute bacterial endocarditis consist principally of masses of fibrin with very few platelets and with minute crevices containing varying numbers of red blood cells. Intermingled in this mass of fibrin are large clumps of bacteria (cocci). Often they extend in dense accumulations over the margins of the leaflets. If thrombi are already formed, the cocci may be found within them in the form of polymorphous areas of "cloudlike" accumulations. They may be covered with fibrin or, less commonly, they may form the most superficial portion of the thrombus. They are often located between the substance of the valve and the thrombus. The lining endothelial cells of the valves early disclose various degenerative changes, eventually become necrotic and finally disappear. Relatively more rarely than is seen in subacute bacterial endocarditis, some of the lining endothelial cells become larger, more cuboidal in shape and contain two or three nuclei. Such giant cells may contain a few cocci within their cytoplasm.

Are the vegetations thrombi? Most observers believe that the vegetations of bacterial endocarditis are thrombi. However, Allen (1939b), because of his interpretation of the histologic evidence, and particularly because of the presence of elastic elements within the vegetations, does not regard them as thrombi deposited from the blood on an inflamed endocardial surface. He believes rather that the vegetations are principally de-

rived from necrotic valvular tissue, forced apart by the plasma and blood elements exuded by the eroded or abnormally permeable blood vessels found in inflamed valves. Moore (1946) also maintained that the vegetations consist of portions of necrotic valvular tissue. It is obvious, therefore, that they consist of thrombi and portions of the necrotic valve, and of the causative microorganism.

Role of bacteria. The cocci obviously mul-

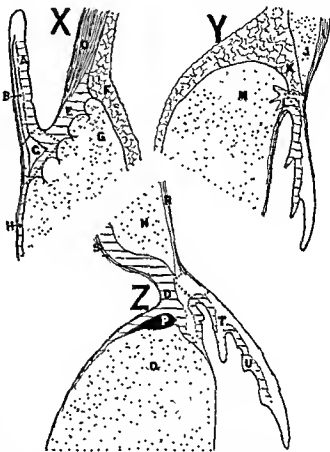


Figure X-9. Diagrams of typical semilunar and atrio-ventricular valve rings.

X. Typical semilunar cusp. A, fibrosa; B, valve spongiosa; C, ring spongiosa; D, aorta; E, annulus; F, pericardium; G, ventricular myocardium; H, subvalvular annulus. Area enclosed by dotted lines is the valve ring.

Y. Typical atrioventricular leaflet; I, atrial myocardium; J, atrial myocardial wedge; K, pericardial wedge; L, annulus; M, ventricular myocardium. Area enclosed by dotted lines is the valve ring.

Z. Typical septal flap of tricuspid valve section. N, right atrial myocardial wedge; O, septum fibrosum; P, bundle of His; Q, interventricular septum; R, right atrial endocardium; S, left atrial endocardium; T, valve spongiosa dipping into insertion of the chorda tendinea; U, valve fibrosa. Area enclosed by dotted lines is the valve ring.

(Reprinted from Gross and Kugel: *Am. J. Path.*, 7:445, 1931, by courtesy of American Journal of Pathology.)

tively rapidly and extend into the substance of the leaflets. Necrosis of various portions of the valve ensues. The necrosis is found first in the region of the ventricularis, the fibrosa of the valve being spared. Only later are all layers of the valve substance involved in the necrotizing process. The necrosis is the result of the bacterial toxins. It may be diffuse; or it may involve certain portions of the leaflet more severely, and thus extend in these localized areas through the entire thickness of the leaflet and cause early perforation.

Inflammatory changes. At first the valvular tissue reacts slowly toward the infection. The principal early changes are necrosis and the presence of cocci. Next, the tissue becomes edematous and fibrin appears, the latter perhaps being an extension into the valve of the fibrin which constitutes the vegetation. Few endothelial leukocytes multiply within the valve. At sites of blood vessels (in old inflamed valves), hyperemia is marked and exudation of polymorphonuclear leukocytes ensues. Most of the leukocytes, however, are found external to the elastic lamellae, indicating perhaps their origin from the passing circulating blood. However, if it is true that blood vessels exist normally at the base of the valve and at the lateral borders of the aortic cusps, as some investigators (Bayne-Jones, 1917; Wearn *et al.*, 1936) maintain, these vessels may be the source of the exudation. Gradually polymorphonuclear leukocytes, fibrin and bacteria form large masses within and adjacent to the valve substance. Still later, more polymorphonuclear leukocytes accumulate at the border between the necrotic valve and the adjacent tissue. In more severe cases, however, the whole cusp or leaflet is involved in the necrotizing process and masses of polymorphonuclear leukocytes also become necrotic. Without staining for elastic fibers, it is often impossible to judge which part of the necrotic mass represents the remains of the valvular tissue and which the necrotic thrombus. The presence of elastic lamellae indicates the remains of valvular tissue. It is easily understood how such masses of necrosis, giving way to intracardiac pressure, are swept

away, with ensuing tearing and ulceration of the valve.

Organization. If the necrosis is not diffuse, early evidence of organization may be noted. Buds of endothelial cells, sprouting from blood vessels at the base, extend into the masses of necrosis with formation of capillary vessels, and young connective tissue cells appear at the margins of the necrosis. As Ribbert stated, the very young blood vessels and rows of fibroblasts extend beneath, and parallel to, the thrombi. Leukocytes migrate from these newly formed vessels, a serous exudate infiltrates the adjacent valvular substance, and fibrin is deposited. Thus, characteristic layers of fibrin appear within the leaflet, with polymorphonuclear leukocytes and monocytes within the meshes of the fibrin (Ribbert, 1924). This material penetrates or surrounds areas of necrosis, extends into the thrombi and eventually forms one mass of granulation tissue.

Sequelae. At the free margin of the vegetation, in both acute and subacute bacterial endocarditis, precipitation of *calcium salts* is early disclosed. Ribbert believed that the deposition of calcium is especially marked in the region of the aortic valves, at the most lateral portions of the cusps where they are attached at the aorta (commissures). This will be more fully discussed later. It seems clear that because of the bacteremia, because of the severity of the valvular lesions, and because of the associated myocardial damage and embolic phenomena, acute bacterial endocarditis is a disease that often causes death in a short time. However, it is conceivable that, in the absence of any complications, even without specific therapy, the organization of the exudate and the granulation tissue of the valve may result in cicatrization with complete healing and resulting deformities. With modern therapeutic measures combatting the bacteremia on one hand and preventing further formation of thrombi on the other, more patients with acute bacterial endocarditis will survive. It should be remembered that old valvular deformities may be the result of acute bacterial endocarditis and that they are

not necessarily always caused by acute rheumatic endocarditis.

Endocarditis without Vegetations. Ribbert (1924) discussed the question whether acute valvular endocarditis can be diagnosed in the absence of thrombi or vegetations. He believed that this is theoretically possible since, adjacent to vegetations, a rough or finely granular valvular endocardium is sometimes seen. Yet, if in very rare cases only such a finely granular endocardium is encountered, microscopic examination invariably discloses flat thrombi consisting principally of fibrin. He, therefore, concluded that endocarditis without verrucae or vegetations does not exist. This statement must be seriously questioned. One sees, not rarely, in association with acute rheumatic endocarditis of the mitral valve, slightly red-tinged, swollen cusps of the aortic valve which seem to have lost their turgor and appear wrinkled. No verrucae are present and the surfaces are glistening. Histologically, such cusps are the seat of edema or of fibrinoid degeneration of the collagen. This condition probably represents very early inflammation of the valve. (See Chapter IX on Rheumatic Endocarditis.) In the absence of verrucae, this inflammation should be termed "acute valvulitis." It is likely that similar changes may be present in very early instances of bacterial endocarditis. Unfortunately, such studies are not available. It might be of interest, therefore, to study microscopically the aortic and mitral valves in instances of acute infectious diseases which grossly show no changes, to determine if early changes may be detected within the valves in the absence of vegetations.

Causative Organisms. Bacterial endocarditis may result from almost any bacteremia or septicemia. It may be incidental to septicemia and of no particular influence upon the course of the disease. It may prolong the septicemia by serving as a secondary focus for the spread of organisms; or it may constitute the principal feature of the disease, and because of embolic complication, cause death.

Karsner (1955) enumerates the following diseases which may be complicated by endocarditis:

pneumonia, osteomyelitis, septicemias and pyemias resulting from wounds and infections incident to childbirth and other causes, typhoid fever, scarlatina, diphtheria, measles, variola, influenza, tuberculosis, gonorrhea, and other infectious diseases. Endocarditis associated with infectious diseases is caused by the organisms of those diseases in some instances, and apparently by secondary invaders in others. Karsner (1955) mentions the following bacteria as being especially associated with acute endocarditis: *Haemophilus influenzae*, the viridans group of streptococci, *Neisseria gonorrhoeae*, *Staphylococcus aureus*, *Staphylococcus albus*, *Diplococcus pneumoniae*, the hemolytic streptococci and *Menningococcus*. Also *Brucella abortus* and higher organisms, such as *Actinomyces* and other fungi, have been reported to have caused endocarditis. Although *Streptococcus* sp. (viridans group) are encountered in the vast majority of instances of subacute bacterial endocarditis, they may also produce acute bacterial endocarditis.

The following table (Table X-3), taken from Thayer (1931), is included here to show the relative frequency of valvular involvement by various bacteria. However, as stated above, both acute and subacute bacterial endocarditis are included in his discussions.

From this table, it is obvious that the *Streptococcus* is the most common cause of bacterial endocarditis. Table X-4 indicates the frequency of involvement of the two sides of the heart in bacterial endocarditis produced by these organisms.

Table X-5 from Moore (1951) is included to show the valves involved by the more commonly encountered bacteria. Both Tables X-4 and 5 indicate that the valves of the left ventricle are much more commonly involved than

TABLE X-3

Causative Bacterium in 306 Instances of Infective Endocarditis, According to Thayer (1931)

Organism	No. of Cases	Per Cent
<i>Streptococcus</i>	191	62.4
<i>Diplococcus pneumoniae</i>	38	12.4
<i>Neisseria gonorrhoeae</i>	31	10.1
<i>Staphylococcus aureus</i>	28	9.2
<i>Haemophilus influenzae</i>	9	2.9
<i>Staphylococcus albus</i>	6	2.0
<i>Pseudomonas aeruginosa</i>	1	0.3
<i>B. anthracis</i>	1	0.3
<i>Klebsiella pneumoniae</i>	1	0.3

TABLE X-4

Causative Organisms in Relation to Frequency of
le of Heart Involved, According to Thayer (1931)

Organism	Left Side	Right Side	Both Sides	Total Cases
<i>epitococcus</i>	78	5	16	99
<i>placoccus pneumoniae</i>	30	3	4	37
<i>phylococcus aureus</i>	18	6	3	27
<i>phylococcus albus</i>	4	2	0	6
<i>isseria gonorrhoeae</i>	17	6	4	27
<i>emophilus influenzae</i>	4	1	2	7
<i>rudomonas aeruginosa</i>	1			1
<i>anthracis</i>	1			1
<i>ebiella pneumoniae</i>		1		1
Totals	153	24	29	206

TABLE X-5

Frequency of Involvement of Various Valves by
veral Common Bacteria, According to Moore (1931)

Valve Involved	<i>Strepto- coccus pyogenes</i>	<i>Strepto- coccus sp. (Vir- dans Group)</i>	<i>Diplo- coccus pneu- moniae</i>	Staphy- lococcus	<i>Neis- seria gonor- rhoeae</i>
aortic	59	51	76	50	70
mitral	76	82	50	43	37
tricuspid	6	3	24	25	10
aortic	20	8	4	4	12

ose of the right. According to Moore, the
ortic valve is the seat of acute bacterial endo-
carditis more often than is the mitral valve,
molytic streptococci cause endocarditis of
ic tricuspid valve relatively often, and the
almonic valve is affected more often by
aphylococci and *Diplococcus pneumoniae*
ian by other organisms.

SPECIAL FORMS OF ACUTE BACTERIAL ENDOCARDITIS

Acute Streptococcal Endocarditis. Strep-
cocci are the organisms most commonly as-
sociated with bacterial endocarditis. It is
usually emphasized that the less virulent
arms of streptococci give rise to subacute
bacterial endocarditis.

In over 90 per cent of cases in Libman and
riedberg's series (1918), the causative organ-
isms were nonhemolytic streptococci, usually of
the alpha (viridans) and only occasionally of the
gamma (anhemolytic) variety. (See also page
31.) Thayer (1931) stated that 60 per cent of

all bacterial endocarditis are caused by strepto-
cocci. He asserted repeatedly that infections
caused by beta-hemolytic streptococci run a
rapid course characteristic of septicemia. Endo-
cardial lesions, either small or large, are present
at the line of closure or free border of the valves
and affect principally the mitral and aortic valves.

Librach (1947) reported an instance of in-
fective endocarditis caused by *Streptococcus sp.*
(Viridans group), involving the aortic and tri-
cuspid valves. No mention was made of older
valvular lesions. Though this instance was classed
as subacute bacterial endocarditis, from the de-
scription it seems more likely that it was an
acute bacterial endocarditis.

Staphylococcal Endocarditis is not rare.
Endocarditis is produced by *Staphylococcus
aureus* more often than by *Staph. albus*.
Thayer emphasized that the course is rapidly
fatal, that often the endocarditis is over-
shadowed by the clinical picture of the gen-
eralized infection and that the endocarditis,
therefore, is rarely recognized clinically, being
discovered only at autopsy. The valves of the
left side of the heart are involved much more
frequently than those of the right side. The
vegetations are soft and usually not large. The
source of the infection, such as osteomyelitis,
puerperal sepsis or a carbuncle, is usually
easily recognized. Often in such infections
metastatic pyemic abscesses are noted, and
they may also be present in the myocardium.
In endocarditis caused by *Staphylococcus
albus* (Figure X-10), endocardial lesions are
more destructive and the vegetations are
polypoid and large. Cobb (1952) described
an infection caused by a coagulase-negative
Staphylococcus albus.

Pneumococcal Endocarditis. The older
literature, but also relatively recent reports
(Allen, 1939a; Coldburgh *et al.*, 1942), stated
that pneumococcal endocarditis involves prin-
cipally the valves of the right side of the
heart.

Thayer's and Moore's tables indicate that this
is obviously not true. Of 37 cases of pneumo-
coccal endocarditis, 30 involved only the left
side of the heart. Of 150 instances reported in
the literature and collected by Tinsley (1915),
117 involved the left ventricle, 17 the right and
16, both ventricles. In 90 of the 117, more de-

tails were available, and the distribution of the endocarditis in these cases is listed in Table X-6. (See Rueggesser, 1938, for pertinent literature.)

TABLE X-6

Frequency of Involvement of Various Valves by *Pneumococcus*, According to Tinsley (1945)

Valve Involved	Number of Cases	Per Cent
Aortic	32	36
Mitral	30	33
Tricuspid	11	12
Aortic and mitral	7	8
Aortic and tricuspid	6	7
Mitral, aortic and tricuspid	1	1
Mitral, tricuspid and pulmonic	1	1
Mitral, aortic, tricuspid and pulmonic	2	2

Tinsley stated that the *Pneumococcus* produces endocarditis in 3 to 3.5 per cent of all pneumococcal infections and is responsible for from 5 to 10 per cent of deaths caused by pneumococcal infections. Karsner (1955) remarked that about 4 per cent of cases of pneumonia develop endocarditis, but in only about one-half of these instances is the *Pneumococcus* found,

other bacteria recovered probably being secondary invaders (Locke, 1924). Applebaum and Bruno (1952) studied 4 cases of pneumonia with complicating endocarditis. In 3 instances the blood culture was positive; *Diplococcus pneumoniae* was found twice and *Staphylococcus aureus*, once.

The vegetations of pneumococcal endocarditis vary in size but often are huge and sometimes cover the entire valvular area. They may be present on the mural endocardium, leaving the valvular endocardium intact. Erosion of the valves with ulcerations (Figure X-7) and mycotic (false) aneurysms occur commonly.

According to Tinsley, pre-existing valvular disease is believed to have little effect on the occurrence of pneumococcal endocarditis. Rueggesser emphasized the occurrence of endocarditis caused by *Pneumococcus* in older persons and Zeman and Siegal (1945) found 4 instances of pneumococcal endocarditis among 9 patients



Figure X-10. Acute bacterial endocarditis caused by *Staphylococcus albus*. Embolism to a small coronary artery. Note necrosis and perforation of wall of vessel and perivascular inflammation. X 135. (WCGH, 46 A 116.)

h acute bacterial endocarditis who were between 60 and 87 years old.

Austrian (1957) reported the triad of meningitis, pneumococcal endocarditis and rupture of a valve. Although he did not specifically elaborate the point, all of his patients had received antibiotic therapy, and it seems that the rupture of a valve was caused by a small valvular aneurysm occurring in the course of a healing acute endocarditis.

Gonococcal Endocarditis. Thayer (1922) pointed out that the anatomic lesions in gonococcal endocarditis were those of a vegetative and ulcerative endocarditis, sometimes spreading to the walls of the ventricles or into the cusps of Valsalva, and often being associated with extensive destruction of valves and with aneurysmal formation. Sometimes the adjacent myocardium also was infiltrated, with resulting purulent myocarditis. The vegetations were large, brittle and yellow-gray.

The aortic valve in Thayer's series (20 cases) was affected 6 times; the mitral valve, twice, and both the aortic and mitral valves, also twice. The mural endocardium of the left ventricle was involved twice, the pulmonic valve was the seat of endocarditis 4 times, and the tricuspid once, with aortic and tricuspid valves were involved once, and aortic, pulmonic and tricuspid valves, twice. Pre-existing valvular disease was present in 20 per cent of Thayer's original series. Among Williams' 10 instances (1938), the mitral valve was affected 5 times; the aortic valve, 4 times; and both valves, once. The valves of the right ventricle were not involved. In a series of 93 instances, combining Thayer's (1931) and Kirkendall's (1932) reports, aortic lesions were present 11 times; mitral lesions, 20; pulmonic, 7; and tricuspid lesions only once. In 24 hearts more than one valve was involved. It is obvious that the left side of the heart is involved much more often than the right side. Yet, Thayer (1931) thought it was significant that among 5 instances without autopsy, 2 showed clinically an apparent involvement of the pulmonary valve, from which impression he concluded that pulmonic involvement seems to be rather characteristic of gonococcal endocarditis. He also quoted a personal communication from Warthin (1931), who found that among 9 patients with gonococcal endocarditis, the pulmonic valve was involved 8 times. His finding is not in agreement with the obser-

vation of other investigators. Thayer (1931) stated that the *Gonococcus* generally attacks previously unaffected valves. Among Williams' 10 hearts, only one disclosed evidence of a pre-existing endocarditis. Karsner (1931), and Hoffman and Taggart (1932) believed that only those instances should be classified as gonococcal which show the presence of gonococci in the blood or vegetations. In spite of this rigid criterion, Williams concluded that gonococcal endocarditis is not rare. Twenty-seven per cent of instances of bacterial endocarditis in his series were attributed to the *Gonococcus*. In fact, Davis (1940) remarked that gonococcal endocarditis is a fairly common disease.

Meningococcal Endocarditis is apparently rare. Whillans (1940) found reports of only 20 cases of meningococcal endocarditis. To verify the diagnosis, the organism should be cultured from the blood, the vegetation, the cerebrospinal fluid or the meninges. The demonstration of intracellular gram-negative diplococci alone is not proof. However, the demonstration of these intracellular gram-negative diplococci in the vegetation of a patient who also shows either the gross characteristic exudate in the meninges or intracellular diplococci within the cerebrospinal fluid seems sufficient for proof, since gonococci practically never localize in the meninges or cause meningitis.

Meningococcal endocarditis may occur as a complication both of meningitis and of meningococcal septicemia. Its occurrence as a primary disease entity (Firestone, 1946) is questionable. Herick (1919) found one instance of endocarditis caused by *Meningococcus* among 208 patients with epidemic cerebrospinal meningitis. MacMahon and Burkhardt (1929) stated that in about half of the cases of meningococcal endocarditis the endocarditis followed meningitis.

Firestone referred to reports of 19 pertinent autopsies; only 3 gave evidence that old chronic valvular disease was present in addition to the acute valvulitis. He also referred to reports of 26 autopsies in which data were given as to the location of the vegetations; the mitral valve alone was involved in 17, the aortic in 3, both these valves in 5, and both the aortic and tricuspid valves in 1. The vegetations were large, massive and yellow-pink, and often covered an entire leaflet. Direct smears usually showed many gram-

negative cocci. Ulcerations are less common than in other types of endocarditis, particularly gonococcal endocarditis. Miller's report (1944) is noteworthy. He found meningococcal endocarditis in immunized horses. He suggested that there is an initial endothelial (endocardial) edema which gives rise to a separation of the endothelial layer from the subendothelial tissue, and that these early changes may be the result of an "alteration in the course of the immunization" which produces an endothelium "more vulnerable to the toxic products" of the Meningococcus. The bacteria later localize on the surface of the damaged endothelium. Whillans emphasized the lack of associated meningitis in his case and in approximately one-half of the cases reported.

Salmonella Endocarditis. Wells (1937) reviewed the literature of endocarditis caused by organisms of the typhoid group. In 320 autopsies of patients with paratyphoid infection, endocarditis was observed only once. He pointed out that typhoid fever and paratyphoid infections rarely cause inflammation of the heart valves. It seems probable that the greater pyogenic tendency of paratyphoid infections may account for endocarditis occurring somewhat more frequently in paratyphoid infections than in typhoid fever. However, too few necropsies of cases of paratyphoid fever are reported to permit conclusive statements.

Meyer and Howell (1938) reported an instance of acute vegetative endocarditis of the aortic and mitral valve caused by *Salmonella paratyphi B*. The endocarditis was superimposed upon old lesions of the aortic and mitral valves, and an early mycotic aneurysm of the sinus of Valsalva was also present. Anderson and associates (1947) reported endocarditis caused by *Salmonella fayed*. Cardiac complications in salmonella infections have been reviewed by Shulman (1947). Stumpe and Baroody (1951) reviewed the literature on *Salmonella* endocarditis and reported a case of bacterial endocarditis caused by *Salmonella oranienburg*. An apparent infection with the organism of type Sendai, with recovery, has been reported by McFadzean and Huang (1952). Massive friable vegetations on the aortic valve with severe ulceration caused by *Salmonella minnesota* were found by Kurz and associates (1949). Fatal bacterial

endocarditis caused by *S. cholerae-suis* was reported by Forster (1939), Read (1939), and Goulder and associates (1942). None of the patients gave a history of gastroenteritis and the portal of entry was not apparent.

Brucella Endocarditis. Scott and Saphir (1928) studied a heart in which acute vegetative endocarditis of the mitral valve was superimposed upon an old endocarditis. Firmly attached to the base of the aortic leaflet of the mitral valve on its atrial surface, was a soft, round, red-gray vegetation measuring 2.5 cm. in diameter. The vegetation partially occluded the already narrowed orifice of the mitral valve. Blood cultures disclosed the presence of *Brucella abortus*. They were not certain that the endocarditis was actually produced by the *Brucella* organisms, but suggested the possibility of brucellemia in a patient who also had acute bacterial endocarditis, even though no other organisms were noted. Levy and Singerman (1938) collected 5 cases of *Brucella* endocarditis from the literature and reported a case in which the endocarditis had involved the mitral valve. The vegetation was large, measuring over 1 cm. in diameter, and was superimposed upon an old endocarditis.

Spink and Nelson (1939) stated that *Brucella* endocarditis is an infrequent complication of brucellosis. It may be caused by any one of 3 varieties of *Brucella*. They reported an instance of endocarditis which had involved the aortic valve and caused a large defect of the posterior cusp. Wechsler and Gustafson (1942) described endocarditis caused by *Br. melitensis* on a congenital bicuspid aortic valve. Whether this was a true bicuspid aortic valve or the result of an old endocarditis (see Koletsky, 1943) cannot be judged from this report. Call and associates (1944) reported 2 additional instances. In one, the endocarditis was present on the aortic valve and in the other, on the mitral valve. They concluded that this type of endocarditis is characterized by the tendency to involvement of the aortic valve, and to ulceration and perforation, and by the association of granulomatous visceral lesions. Degowin and associates (1945) found the free margins of the mitral leaflets moderately fibrosed. The anterior leaflet of this valve had a perforation measuring 7 mm. in diameter. At the superior margin of the perforation was a friable gray-yellow vegetation 1 cm. in diameter. Smaller but similar vegetations were attached at the periphery of the perforation. Several small, firm yellow pebbled masses were found along the re-

inder of the line of closure. In Beebe and neely's (1949) case a recent endocarditis was superimposed upon an old endocarditis. *Brucella* was isolated in pure culture during life directly from the blood stream and, after death, in the vegetations of the valve. The patient died from rupture of a mycotic aneurysm of the femoral artery. Crant and Stote (1953) noted that *Brucella abortus* endocarditis was reported only twice in England, but found 21 cases reported from other countries. They noted a tendency to ulceration. Their patient died as a result of rupture of a small abscess in the wall of an aneurysmal dilatation of the sinus of Valsalva. The patient of Hart and associates (1951) had aortic valvulitis. These authors also stressed the tendency to ulceration and to formation of mycotic aneurysms.

Endocarditis Caused by *Pseudomonas aeruginosa*. Fish and associates (1937) studied an instance of infection with *Pseudomonas aeruginosa* (*B. pyocyaneus*) associated with bacterial endocarditis. They believed that such an endocarditis is rare. (Consult Fish *et al.* for literature.) Many of these infections have been reported in children. They stated that the most interesting feature of this infection is the affinity of the organism for the wall of arteries. They described a yellow-red, shining mass, measuring 75 cm. in diameter, attached quite firmly to the aortic valve and present on both the aortic and mitral aspects of the cusp. There was also acute aortitis but no old lesions in the valves. Oragues and Anderson (1943) reviewed the literature and reported an additional instance of endocarditis caused by *Pseudomonas aeruginosa*. They emphasized the importance of the genitourinary and gastrointestinal tracts as portals of entry. Waisbren and Hastings (1953) reported a pertinent case and insisted on the following criteria in accepting these organisms as causative: The clinical picture must be compatible with endocarditis; the organisms must be isolated from the blood several days before death, and the bacilli must be demonstrated in the heart valves or microscopic section. Judged by these criteria, the authors believed that their case was the fifth proved case on record. Collier and Dyer (1951) studied a case in which the primary infection appeared to have been in the lung. Andersen and Jensen (1956) reported 3 cases of bacterial endocarditis following mitral valvotomy. The organisms were *Staphylococcus aureus*, *Staphylococcus albus* and *Pseudomonas pyocyanea*, respectively.

Endocarditis Caused by Other Organisms. Craven and associates (1940) reviewed 36 cases of endocarditis caused by *Hemophilus influenzae* and *H. parainfluenzae* (Pfeiffer) and reported 2 cases of endocarditis caused by *H. parainfluenzae* (nonhemolytic). In most of the instances of endocarditis reported to have been caused by *H. influenzae*, in retrospect, *H. parainfluenzae* could not be ruled out as the causative agent. They felt that the endocardial vegetations are of the vegetative ulcerative type and are often, but not always, superimposed on old rheumatic valvular lesions. In 5 of the 36 cases reviewed, there was unmistakable clinical or necropsy evidence of meningitis. They concluded that the high incidence of meningitis, which was often distinctly chronic, suggested that the infection of the leptomeninges antedated the endocardial lesions. Tenczar and associates (1951) encountered endocarditis of the pulmonary valve, caused by *H. parainfluenzae*; the patient also had congenital aneurysms of the sinuses of Valsalva.

An instance of a bacterial endocarditis interpreted as resulting from *H. haemolyticus* and *Streptococcus sp.* (Viridans group) infection was reported by De Santo and White (1933).

Fletcher (1947) reviewed the literature on endocarditis caused by *E. coli*. He emphasized the proliferative nature of the vegetations, that the infection usually occurs as a postoperative complication, and that it may attack a normal valve. Ross and associates (1952) pointed out that the usual portals of entry for this organism are the gastrointestinal tract, the urinary tract or the female genital tract. In their case, it seems that a mixed pulmonary infection with type III *Diplococcus pneumoniae* and *E. coli* was the source of the initial bacteremia. Wallace (1951) collected 13 cases of *E. coli* endocarditis. He also reported an instance of *Aerobacter aerogenes* endocarditis with associated urinary tract infection, and gave a brief review of the pertinent literature. A case of massive vegetative endocarditis of the pulmonary valve caused by a *Paracolonobacterium sp.* was reported by Robertson (1947) (Consult Robertson for literature on endocarditis produced by these organisms.) The other cardiac valves were normal. It was thought that the valvular lesion and the septicemia were secondary to infected polycystic kidneys.

An apparently unique instance of bacterial endocarditis caused by *Clostridium perfringens* has been reported by More (1943). Instances of bacterial endocarditis in which two or more organisms were cultured repeatedly from the

patient's blood have been collected by Orgain and Poston (1942). Endocarditis caused by *Alcaligenes fecalis* (*B. alcaligenes*) has been recorded by Cole and Marshall (1952). Hawe and Hughes (1954) studied an instance of endocarditis caused by *Chromobacterium prodigiosum*, the posterior leaflet of the mitral valve was affected.

For reports on endocarditis caused by *Micrococcus pharyngis siccus* (*Neisseria sicca*) and related organisms, see Weed and associates (1943).

Lewisohn (1957) reported the rare occurrence of acute endocarditis as a result of infection with *Micrococcus tetragenus*; in his patient only the pulmonic valve was affected.

During recent years bacteria of the tribe genus *Mimcae* have been isolated from various lesions. The *Mimcae* are a loosely defined group of pleomorphic gram-negative cocci, diplococci and rods. The tribe consists of three genera: *Mimca*, *Herellea* and *Collaides*. Sorrell and White (1953) reported acute endocarditis caused by a variant of the genus *Herellea*.

MYCOTIC ENDOCARDITIS

Cassels and Steiner (1944) critically reviewed the available literature on mycotic endocarditis. Primary infection of the endocardium with higher organisms was distinctly uncommon.

In a 14-year-old white boy, the mitral valve contained an almost continuous row of vegetations which were rough and warty, mottled yellow and red, and were friable but firmly attached. The aortic valve had a single large vegetation. There were no old valvular lesions. Colonies of microorganisms were found scattered throughout the vegetations. The organisms took the form of long, slender filamentous branching rods or of small, round or oval bodies, and both forms were gram-negative and not acid-fast. Such microorganisms were also found in myocardial and epicardial abscesses, in an infarct of the spleen, in small renal foci of suppuration and in the intestines. While the organisms could not be specifically identified, the authors pointed out that the appearance of the growth on culture and in microscopic sections was the same. There was no evidence that the fungus infection could have been superimposed on a previous bacterial infection.

Beamer and associates (1945) reported 2 cases of vegetative endocarditis, 1 caused by

Actinomyces graminis and the other by *Histoplasma capsulatum*. In the former the mitral and aortic valves were moderately thickened and the seat of numerous firm, gray-white vegetations. On microscopic examination the organisms were pleomorphic. The second case disclosed a thickened aortic valve with a friable vegetation involving both its ventricular and aortic surfaces. *Histoplasma* was recognized in macrophages. A syphilitic aortitis which had extended to the aortic valve was also noted. These authors reviewed instances of vegetative endocarditis caused by higher bacteria, yeasts and fungi, including *Candida* (*Monilia*), *Actinomyces*, *Leptothrix*, *Erysipelothrix* and *Histoplasma*. Wedding (1947) reviewed the literature and described 2 instances of actinomycotic endocarditis; 1 was characterized by the clinical picture of subacute endocarditis, but the other was not recognized clinically. Blevins and MacNeal (1946) recovered *Actinomyces* from 2 patients. In 1 patient with bacterial endocarditis, a branching filamentous organism in cultures was obtained on 4 occasions. This organism exhibited the characteristics of a micro-aerophilic *Actinomyces*, was irregularly gram-positive and not acid-fast. It was termed *Actinomyces septicus*. Large vegetations were situated on the mitral valve which was ulcerated, and the myocardium disclosed acute focal inflammation. Cultures from the mitral valve showed various coccoid organisms, and inoculation of the organism into a rat resulted in infection of the animal and recovery of *Actinomyces* in pure culture. The second patient presented the clinical picture of subacute endocarditis. Friable, verrucous structures were found on the aortic cusps, and separate filaments were seen in necrotic portions of the aortic and mitral valves. An anaerobic strain of *Actinomyces* was recovered from vegetations of the aortic valve. Stokes and associates (1951) remarked on the similarity to the clinical picture of subacute bacterial endocarditis in their case of endocarditis caused by *Streptobacillus moniliformis* (*Actinomyces visus*).

Endocarditis caused by *Nocardia albicans* (*Candida albicans*) was found superimposed on a healed (subacute bacterial) mitral endocarditis by Geiger and Durlacher (1947). Recent vegetations involved the chordae tendineae of the mitral valve and the left atrial endocardium. Endocarditis caused by *Nocardia albicans* in an infant was recorded by Kunstadter and associates (1952); infection caused by *Nocardia flava* (*Aspergillus flavus*) was reported by Kirsch-

stein and Sidransky (1956). We have also seen several instances of fungus endocarditis in patients who had received antibiotics for various reasons prior to the final illness. It is possible that treatment with antibiotics renders the more common bacteria innocuous and paves the way for infection with certain mycotic organisms.

Merchant and associates (1956) reviewed 31 instances of fungus endocarditis and reported 3 additional cases (2 associated with *H. capsulatum* and 1 with *C. immitis*). They stated that the diagnosis of fungus endocarditis should be entertained clinically if the patient presented the picture of subacute bacterial endocarditis but had repeated routine sterile blood cultures, and evidence of a systemic mycotic infection elsewhere as indicated by positive culture of urine, bone marrow, lymph nodes, or other material.

Cryptococcus neoformans also may rarely cause endocarditis. Lombardo and associates (1957) reported an instance in a 44-year-old coal miner. Polypoid vegetations were present on the mitral and aortic valves. These contained numerous cryptococci interspersed in a mesh of fibrin, together with an eosinophilic and basophilic debris, and also calcareous deposits, macrophages, polymorphonuclear leukocytes and lymphocytes.

ENDOCARDIAL TUBERCULOSIS

The tubercle bacillus may cause endocarditis. Baker's article gives an excellent résumé of reported infections up to that time (1935). His own observations are based on 7 instances. He classified endocardial tuberculosis as follows: (1) endocardial tubercles in miliary tuberculosis, (2) polypoid tubercles, (3) tuberculous nodules on the valves, and (4) tuberculous thrombi. In the last form, it is thought that tubercle bacilli are trapped in a thrombus, and that the thrombus is then transformed into tuberculous granulation tissue. However, it is more likely that most of the "tuberculous thrombi" recorded were tubercles primarily and that thrombi formed secondarily.

Criteria for Diagnosis. The diagnosis of tuberculous endocarditis should be accepted only if (a) microscopic sections are characteristic of a tuberculous lesion, (b) tubercle bacilli are demonstrable in the lesion, and (c) other causes of endocarditis are excluded.

Neither the presence of tubercle bacilli in the blood nor the demonstration of widespread tuberculosis elsewhere in the body should be taken as evidence of the tuberculous nature of the endocardial lesion.

Origin. Scattered tubercles of the endocardium may arise by implantation through the coronary arteries or directly from the circulating blood, and by extension from pericardial or myocardial tuberculous masses.

Dressler (1921) tells of a child with generalized miliary tuberculosis in whose heart he found a polypoid excrescence on the aortic leaflet of the mitral valve. On microscopic examination this proved to be typical tuberculous granulation tissue. He classified this infection as a primary tuberculous endocarditis. He quoted Weigert as saying that miliary tubercles are almost always present in the myocardium in instances of generalized miliary tuberculosis. This opinion, however, is not generally accepted. Two instances of tuberculous endocarditis were reported by Davie (1936). Vegetations resembling the verrucae of rheumatic endocarditis were found on the mitral and aortic valves in one, and only on the mitral valve in the second instance. Davie assumed the existence of a tuberculous "allergic" endocarditis.

Bevans and Wilkins (1942) found tuberculous endocarditis of the mitral and aortic valves. The aortic valve was also congenitally malformed. In addition to the characteristic granulation tissue, large numbers of eosinophils were present. This finding, they believed, supported Davie's hypothesis. Mark (1938) found a tuberculous polypoid vegetation on a cusp of the pulmonary valve in a patient with generalized miliary tuberculosis. Gilmore (1940) found within the sinus of Valsalva of the right anterior cusp of the pulmonary valve a yellow, firm, irregularly shaped mass firmly adherent to the proximal portion of the cusp. On microscopic examination this mass consisted of typical tubercles with central areas of necrosis surrounded by small round cells, endothelial leukocytes* and giant cells. The process involved the valve ring

* The term "endothelial leukocyte" (Mallory) denotes the large mononuclear phagocyte, a cell almost as ubiquitous throughout the tissues of the animal body as the connective tissue itself, and one reaching prominence in many inflammatory exudates. It is pre-eminently phagocytic in function. Other terms used for endothelial leukocyte are "epithelioid cells," "polyblast," "clasmatoocyte," "histiocyte."

but did not extend into the myocardium. Acid-fast bacilli were demonstrated in the valvular lesions. The patient had advanced tuberculosis of the prostate, dorsal vertebrae and lungs, with terminal miliary dissemination.

Symptoms. Tuberculous endocarditis *per se* may produce no clinical symptoms (Dressler, 1921). In tuberculous valvulitis, there is no special predilection for the line of closure. The cardiac function is affected only in rare instances in which caseous nodules involve the valves.

TOXINS AS CAUSE OF ENDOCARDITIS

Ribbert (1924) discussed the possibility of bacterial toxins causing endocarditis. While this is denied, he believed that it is possible that toxins may injure the valves and cause loosening of the valvular endothelial cells, with degenerative changes and subsequent repair. There is, perhaps, a resulting cellular proliferation but no outspoken endocarditis. These changes are sometimes encountered in diphtheria and typhoid fever. Ribbert did not believe that a vegetative endocarditis can possibly be superimposed on these changes in the absence of microorganisms. Though there are experimental data regarding sensitization of valves with various products of bacteria (see Chapter IX on Rheumatic Disease), it is remarkable how little is known concerning the role of toxins in endocarditis. In rare reported instances of endocarditis in diphtheria, either there was a bacteremia (*Corynebacterium diphtheriae*) or the endocarditis was caused by secondary invaders from the upper respiratory tract. Pike (1951) reported bacterial endocarditis apparently caused by *C. diphtheriae* and referred to a few similar cases in the literature. The blood cultures were positive, but the patient showed no clinical evidence of diphtheria. The portal of entry was not found. Investigation of this subject might be fruitful. There are also instances on record of endocarditis in *virus diseases*, e.g., smallpox (Ribbert, 1924; Karsner, 1955). Before the discoveries of the causative viruses, such forms of endocarditis were thought to be the result of bacterial toxins. There are also forms of endocarditis classified as nonbacterial. Whether some of these are caused by toxins is difficult to decide.

MECHANISMS OF LOCALIZATION OF VEGETATIONS

Allen (1939a) made an extensive study of

the mode of development of bacterial endocarditis in general, and much of the following is taken from his publications. It is possible that a similar mode of localization of the vegetations also holds for subacute bacterial endocarditis. Several views are given in the literature. Some authors maintain that bacteria reach the valve through its blood vessels by way of the coronary arteries (Coombs, 1909). The pertinent question is whether blood vessels are present in normal valves.

Are Blood Vessels Present in Normal Valves? Bayne-Jones (1917) concluded that blood vessels normally occur in the valves of the heart and that his failure to detect them in all hearts was probably caused by imperfect technique and lack of proper conditions. He also pointed out that the lateral portions of the semilunar valves are supplied with blood vessels which extend through the commissures, while the central portions of these valves do not disclose blood vessels.

In 1921 Gross, in a monograph on the blood supply of the heart, concluded that all fetal valves possess vessels. Usually, some time before birth, the blood vessels undergo regression; in a small percentage of persons, however, there is a persistence of blood vessels to adult life. He believed that this persistence predisposes an individual to embolic valvular endocarditis. Kugel and Gross (1925) several years later, on the basis of further examinations, believed that blood vessels exist in some valves in a small percentage of hearts other than those of fetuses, that these are of developmental and not inflammatory origin, and that they occur most frequently in the aortic leaflet of the mitral valve. Such vessels may exist in either a complete or incomplete form.

Ritter, Gross and Kugel (1928) studied 700 human hearts with reference to the existence of blood vessels in the valves. Among these, 14 normal hearts were found which presented blood vessels in some of the valves. They stated that thorough clinical and pathologic examination had failed to reveal that these vessels owe their origin to inflammation. In a subsequent study, Gross (1937) reported that blood vessels do not exist in normal valves at all; or if they do, they must be extremely rare. He pointed out that in those instances where blood vessels were present in the heart, widespread stigmata were histologically evident, bearing striking resemblance to

those seen in hearts of patients with old rheumatic endocarditis. He believed that an endocarditis of low grade may heal so completely as to leave only blood vessels in its wake. Wearn and associates (1936) found blood vessels in the valves in 86 of 100 hearts of patients who had no history or clinical evidence of endocarditis. They emphasized that 12 of these hearts showed evidence of active or healed valvulitis. Their studies were based on a special method of injecting the coronary blood vessels. Wearn and Moritz (1937), in their study of 235 hearts with no apparent inflammation, found blood vessels in the mitral valve in 50 per cent, in the tricuspid valve in 31 per cent, in the aortic valve in 5 per cent, and in the pulmonic valve in 4 per cent. From this short review, it is clear that there still is no agreement as to whether blood vessels exist in normal heart valves.

Relation of Blood Vessels to Old Inflammation. From the study of the literature, one gains the impression that, rarely, vascularization may occur in either normal valves or valves that were the seat of an inflammation and had healed so completely as to leave practically no evidence of inflammation. Perhaps only those hearts in which the valves previously had been vascularized will eventually become involved in endocarditis, but this possibility has not yet aroused sufficient interest to make it a subject for study.

The fact that a primary embolus or primary accumulations of bacteria in blood vessels of the valves have never been demonstrated speaks against the embolic theory of acute bacterial endocarditis. Also, because blood vessels were found by Wearn and Moritz (1937) in the tricuspid valve in 31 per cent of hearts and in the aortic valve in only 5 per cent, one would expect the tricuspid valve to be more frequently involved by endocarditis than the aortic valve, but of course this is not the case. Besides, as stated above, Gross in his later studies questioned the occurrence of blood vessels in normal valves. We also have no explanation why emboli should be carried principally to the valves of the left side of the heart rather than to the myocardium or mural endocardium.

Role of Trauma and Strain. A favored theory explaining the localization of bacteria on the valves concerns itself with the formation of eddy currents in the region of the

lines of closure. Allen (1939a) pointed out that the sites of eddy currents are the areas between the superior surface of the semilunar valves and the great vessels, and between the ventricular surface of atrioventricular valves and the wall of the ventricle. However, these areas are only exceptionally the seat of primary vegetations. It was also thought that the line of closure of the valves is so often the seat of the vegetations because of the trauma and strain caused by mechanical impingement of the margins against each other. Allen tried to show that, after apposition of the leaflets has taken place, the trauma from closure is far less than that produced by edges which have been slapped together in the manner generally conceived. Therefore, he believes, that the impingement theory seems inapplicable not only for lesions of the normal valve, but also for the great majority of lesions superimposed on diseased valve leaflets, the margins of which are physically unable to impinge on each other.

Experimental Lesions. Nedzel (1936) was able to produce endocardial lesions by the injection of Pitressin with, and sometimes without, subsequent injection of bacteria. He thought that the pressor effect thus produced causes the valve to exude from its surface a stringy, adhesive substance to which bacteria adhere. He believed that during such pressor episodes the margins of the leaflets impinge on each other more forcefully. However, as stated above, there is little probability that the theory of impingement *per se* is correct; furthermore, acute bacterial endocarditis has been produced in animals after a single injection of virulent bacteria, obviously without the aid of pressor episodes (Blahd *et al.*, 1939).

Local Degeneration. Degenerative changes have been described in deformed valves, giving rise to platelet thrombi which in turn may lead to localization of bacteria (Grant *et al.*, 1927). This is often attributed to local susceptibility because of an acquired altered reactivity of the tissue (Semsroth and Koch, 1930). (See also Chapter IX on Rheumatic Endocarditis.)

Factors in Localization. Allen (1939a) pro-

posed an explanation of the mechanism of localization which satisfies 4 universally recognized points: (1) Bacterial endocarditis is often superimposed on a fibroblastic deformity; (2) congenital lesions are particularly susceptible; (3) there is a distinct preponderance of lesions on the left side over those on the right; and (4) bacterial endocarditis is rare in patients with atrial fibrillation secondary to stenosis of the mitral orifice. He believed that a pre-existing valvular fibroblastic deformity often takes the form of a projecting shelf or barrier against which the blood strikes. Because of this obstruction to the systolic discharge, the site of the deformity suffers a great impact, the resulting trauma favors the localization of bacteria. Allen also stated that there seems to be a greater tendency for the virulent rather than the relatively avirulent organisms to invade the right side. Thus, the valves of the right side of the heart, though previously not diseased, may become involved in bacterial endocarditis as a result of the presence of highly virulent organisms. He believed that bacteria are prone to localize on the outflow surfaces of the valves because the outflow surfaces of all valves come in contact with a much greater volume of blood and of toxic agents than do the inflow surfaces. Because in atrial fibrillation forcible ejection into the ventricle does not occur, bacteria are not likely to settle on the leaflets of a stenosed mitral orifice. However, the possibility of the influence of other auxiliary factors, he stated, are not precluded.

Evaluation. In spite of Allen's logical discussion, a number of questions still remain unanswered. Why does one encounter, not rarely, bacterial endocarditis developing on normal valves of the left side of the heart? It is possible to produce in experimental dogs acute bacterial endocarditis with a single injection of microorganisms (Blahd *et al.*, 1939). Dick and Schwartz (1946) also recently produced endocarditis in dogs that had no previous injury of the cardiac valves. In regard to the virulence of the organisms, they stated that, whereas more virulent strains produce endocarditis in shorter time and with fewer injections than do less virulent strains,

it is necessary only to continue the injections with avirulent organisms for a longer time and with increased doses. As will be discussed later, endocardial pockets and circumscribed areas of endocardial fibrosis projecting into the left ventricle are not particularly rare. Such areas are also exposed to the force of the blood stream and pressure. Such pockets do occur in instances of older valvular lesions and in acute and subacute bacterial endocarditis. And yet, these pockets or endocardial fibrous plaques are extremely rarely the seat of vegetations. (See case report by Allen, 1941.) It seems that all the above-mentioned factors under various circumstances may play a role in the localization of the vegetations. Also, trauma, produced by abnormally directed columns of the blood stream as a result of congenital anomalies, must be considered.

Fudong showed that, in such an instance, vegetations developed not at the site of the congenital defect but at the site of the trauma. Against Allen's (1939b) hypothesis, it must also be argued that atrial fibrillation does occur in acute and subacute bacterial endocarditis with stenosis of the mitral orifice and is definitely not as rare as was previously supposed (de la Chapelle and Graef, 1932; McDonald, 1946). Thus, the argument that forceful contraction of the left atrium is necessary for the production of acute or subacute bacterial endocarditis does not hold. One must also consider the virulence of the agent, the resistance of the host and of the valvular area, perhaps the altered reactivity of the latter, and factors linked with local tissue response. Perhaps too much emphasis is placed on the presence of pre-existing deformities of the valves rather than on whether the valves were vascularized prior to the onset of the acute endocarditis. Experimental work indicates that a chronically overloaded heart is susceptible to valvular damage. In rats exposed to the equivalent of very high altitudes, nodular thickenings developed on the heart valves following repeated administration of non-hemolytic streptococci, and acute endocarditis resulted more frequently than in controls. Similar results have been produced in dogs with arteriovenous fistulas (Highman and Altland, 1949, 1950). (See also Bobb and associates, 1952.) Thus, it is evident that, in association with a bacteremia, a number of factors

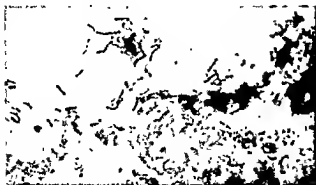


Figure X-11. Subacute bacterial endocarditis. Streptococci in superficial portion of vegetation.

determine whether endocarditis will occur. (See also Experimental Endocarditis, page 751.)

Subacute Bacterial Endocarditis (Endocarditis Lenta)

Designation of Endocarditis as Acute and Subacute Forms. Bacterial endocarditis is usually designated as acute bacterial and subacute bacterial endocarditis. This terminology is based on the duration of the disease and is significant from the clinical point of view. Acute bacterial endocarditis generally lasts less than six weeks. In studying a number of reports of acute and subacute bacterial endocarditis, generally no clear-cut differences are pointed out between these two forms. There are many transitional forms in which, from the data on hand, no distinction can be made, and it remains often a matter of personal preference whether to classify the endocarditis as acute or subacute. This is, of course, particularly true when acute bacterial endocarditis is superimposed on an old valvular lesion. To judge from the literature, it would seem that in some such instances the clinical picture of subacute bacterial endocarditis is more likely to lead to the diagnosis than are the anatomic features. A number of articles and monographs, labelled "bacterial or infective endocarditis," deal with both acute and subacute bacterial endocarditis. It is confusing when in such communications the results of bacterial studies, the age incidence, the duration of the disease, and the gross anatomic and histologic findings of both types of endocarditis are discussed under one heading. This would be justified if acute bacterial

endocarditis were an early stage of a later-developing endocarditis lenta. The point in question is whether acute bacterial endocarditis is one entity and subacute bacterial endocarditis (endocarditis lenta) is a different, well-defined entity or disease. Are acute and subacute bacterial endocarditis two diseases? Does subacute bacterial endocarditis or endocarditis lenta start as acute bacterial endocarditis? Is it possible from the gross and histologic picture alone to distinguish between acute bacterial and subacute bacterial endocarditis? Knoll (1941) pointed out the difficulties of classifying anatomic lesions under the heading of subacute bacterial endocarditis in the light of expert opinion and recent experimental work.

Before a discussion of these questions is undertaken, a few data in regard to age distribution, involvement of various valves, and a description of the gross and microscopic appearance of subacute bacterial endocarditis will be given.

Age Incidence. The age distribution of subacute endocarditis was given by White (1951), from a study of 250 cases, as follows: Six patients were under 10 years of age, 42 between 10 and 20, 79 between 20 and 30, 53 between 30 and 40, 39 between 40 and 50, 21 between 50 and 60, and 10 over 60.

White also stated that the youngest patients on record were 1½ years, 2½, and 5 years old. He remarked that this disease is very rare in young children. In Seabury's (1947) series of subacute bacterial endocarditis, 55.8 per cent of the patients were found to be in the third and fourth decades. Libman and Friedberg (1948) stated that two-thirds of their patients with subacute bacterial endocarditis were between 20 and 40 years old. In the report of Clawson (1941), among 30,265 autopsies, 514 cases of bacterial endocarditis were encountered; in 364 instances, symptoms had lasted more than 6 weeks. Of the 364 persons, 237 were males and 127 females. Six patients were in the first decade, 35 in the second, 83 in the third, 81 in the fourth, 71 in the fifth, 48 in the sixth, 33 in the seventh, 4 in the eighth, and 3 were in the ninth decade. Zeman (1945) found subacute bacterial endocarditis in 8 patients whose ages were between 60 and 87 years.

TABLE X-7

Frequency of Involvement of Valves and Mural Endocardium in 50 Patients with Subacute Bacterial Endocarditis (Denman, 1942)

Valves and/or Mural Endocardium Affected	No. of Hearts Affected
Mitral	21
Aortic	10
Pulmonic	1
Tricuspid	1
Mural endocardium	2
Mitral, aortic and tricuspid	1
Mitral and aortic	3
Mitral and tricuspid	2
Mitral and mural endocardium	4
Aortic and tricuspid	2
Mitral, aortic and mural endocardium	1
Aortic and mural endocardium	1

TABLE X-8

Organisms Recovered on Blood Culture from 157 Patients with Subacute Bacterial Endocarditis (Seabury, 1947)

Organisms	Number	Per Cent
<i>Streptococcus sp.</i> (Viridans group)	126	80.2
<i>Streptococcus pyogenes</i>	3	1.9
<i>Streptococcus sp.</i> (gamma hemolytic)	12	7.6
Gram-positive cocci in chains	3	1.9
<i>Gaffky tetragena</i>	1	0.6
Gram-negative pleomorphic rods	1	0.6
<i>Staphylococcus albus</i>	1	0.6
<i>Staphylococcus aureus</i>	1	0.6
<i>Brucella abortus</i>	1	0.6
<i>Clostridium</i>	1	0.6
Absent in life, present at autopsy	7	4.5

Valves Involved. Table X-7 presents the frequency of involvement of the various valves and of the mural endocardium in Denman's (1942) series of 50 cases. (One of Denman's cases is not included since apparently only the epicardium was involved.)

Among 1000 consecutive autopsies performed at Michael Reese Hospital on patients over 2 years of age, subacute bacterial endocarditis was encountered 15 times. The mitral valve alone was involved 3 times, the aortic valve 5 times, and both valves 7 times.

Causative Organisms. In the vast majority of cases, *Streptococcus sp.* (Viridans group) (alpha hemolytic *Streptococcus*) was found to be the causative agent (Figure X-11).

Moore (1951) stated that this organism is the cause in about 95 per cent of his cases. Table X-8 lists the organisms recovered by Seabury (1947)

on blood culture from 157 patients with subacute bacterial endocarditis. Libman and Friedberg (1948) mentioned, among other causative organisms, members of the genus *Neisseria*, such as (*Diplococcus pharyngis siccus*) *Neisseria sicca* and *N. catarrhalis*, as well as *Corynebacterium sp.*, *Spirillum surati*, *Streptobacillus moniliformis* and others. Jones (1950) reviewed the literature from 1936 to 1948, inclusive, of cases of subacute bacterial endocarditis of nonstreptococcal etiology. Subacute bacterial endocarditis has rarely been reported to have been caused by *Klebsiella pneumoniae* (Friedlander's bacillus). Thayer (1931) mentioned only one such infection. In a number of reports of supposed subacute bacterial endocarditis, it is not clear whether the infections actually represent acute bacterial endocarditis superimposed on old valvular lesions. Thus, Matthew (1951) demonstrated a coagulase-negative *Staphylococcus albus* in his case, Goudie and Lowther (1951) both *Haemophilus parainfluenzae* and *Streptococcus sp.* (Viridans group), Fairbrother and Lord (1952), *Streptococcus pyogenes* (Str. hemolyticus); Roberts and Goldberg (1951), enterococci; Wood and associates (1955), *Streptococcus lactis*; and Dietzsch (1955), lactobacilli. Herrell and Heilmann (1952) emphasized that more than 90 per cent of the cases of subacute bacterial endocarditis are caused by streptococci which produce a green color or are indifferent in color on blood agar, and that these organisms include a number of different species, the most common of which are *Str. salivarius*, *Str. mitis* and *Str. faecalis*.

Bacteria, however, are not always demonstrable in certain clinically clear-cut cases of subacute bacterial endocarditis, either post mortem or during the course of the disease, although they had been previously recovered in blood cultures and no specific treatment had been given. Libman (1913), therefore, divided subacute bacterial endocarditis into a bacterial and an abacterial stage. In the abacterial stage, no organisms are recovered from the blood stream or the vegetations. In this stage, the patient may succumb to renal insufficiency or to the effects of embolism. Libman and Friedberg believed that bacterial cultures are negative in the so-called bacteria-free stage because bacteria are then no longer present on the surface of the endocardial vegetations and, therefore, none appear in the blood stream. However, it is also likely that abundant antibodies in the blood stream may cause bacteria to be precipitated, so that they



Figure X-12. Early vegetations in subacute bacterial endocarditis superimposed on old rheumatic valvulitis. (WCCB, 45 P 283.)

may localize on the cardiac valve. It has often been maintained that patients with bacterial endocarditis possess various immune bodies which are able to destroy the organisms. Only if bacteria enter the circulating blood faster than immune bodies can destroy them, may they be demonstrable in blood cultures.

Portal of Entry. Weiss (1934) pointed out that the portal of entry of the bacteria in subacute bacterial endocarditis is most often the upper respiratory tract. However, subacute, like acute bacterial endocarditis, has also been reported in association with a number of diseases. Not rarely this disease has been observed following dental extraction.

Of 92 instances of subacute bacterial endocarditis reviewed by Barnfield (1945), in 6 extraction of teeth was associated with the disease. A study of these instances suggested that extraction either may have caused the endocarditis or, in those cases in which extraction had been performed after the onset of the endocarditis, may merely have been the apparent cause of the infection. He concluded that there is evidence that post-extraction bacteremia causes the subacute bacterial endocarditis.

The most frequently associated or preceding disease is rheumatic fever. This will be discussed subsequently.

Gross Distinction from Acute Bacterial Endocarditis. In some cases, clear-cut gross distinction between acute bacterial endocarditis and subacute bacterial endocarditis can be made with relative ease. The diagnosis of acute bacterial endocarditis is not difficult if the recent vegetation is massive and if it is imposed upon a valve which shows no evidences of older inflammation; in other words, if the valve is tender and delicate. As pointed out previously, the vegetations may also be present on the adjacent mural endocardium, and large ulcers are not rare. It seems obvious that such an endocarditis must be designated as acute vegetative endocarditis and, because of the presence of bacteria which invariably are easily demonstrated, as acute bacterial endocarditis. If engrafted upon an old endocarditis, the latter is characterized by old scarring with retraction of the cusp, or adhesions between the cusps. In typical subacute bacterial endocarditis, the vegetations are also large but not massive, and their coloration contains more gray or yellow than red. They are often vermiform in appearance. The endocarditis often extends beyond the limits of the leaflets and the mural endocardium is invariably involved. Minute ulcerations, never large ones, are present in ad-

jacent free margins of thickened leaflets, giving them a moth-eaten appearance. Tearing of the involved valves may occur. The cusps or leaflets always show evidence of an older endocarditis. These older lesions may be characterized only by slightly thickened free margins of the cusps or leaflets (Figure X-12), or rolled edges or moderate retraction of the cusps. Occasionally, adhesions of a slight degree may be found between the cusps. Old healed lesions with marked fibrosis, hyalinization, and calcification are usually not present. Parietal lesions occur predominantly in the left atrium and left ventricle. Fibrous irregularities, as a result of healing, often assume a characteristic coarse "sharkskin" appearance. The organism present in the vast majority of cases of subacute bacterial endocarditis is *Streptococcus* sp. (Viridans group). The histologic finding of many cocci in the valves is not sufficient for diagnosis. From a practical point of view, it may be wise to remember that if a majority of the following factors are present, the case

in question is likely to be subacute bacterial endocarditis rather than acute bacterial endocarditis: (1) evidence of an older endocarditis, without old calcific changes; (2) long vermiform vegetations and small ones, side by side; (3) minute ulcers, with "moth-eaten" free edges of the cusps; (4) involvement of the mural endocardium; and (5) presence of *Streptococcus* sp. (Viridans group).

Microscopic Changes. Jaffé (1932) gave an extensive description of the histologic changes in the valves of subacute bacterial endocarditis. The vegetations usually consist of fibrin, platelets and polymorphonuclear leukocytes, the masses of fibrin being most pronounced on the surface of the vegetations (Figure X-13). Minute foci of calcification are not rare. Though Jaffé believed that the cocci *per se* become calcified, later studies of healing endocarditis make it seem more likely that lime is deposited within the necrotic portions of the vegetations, close to their edges. Necrotic portions of the valve leaflets are found adjacent to large or small



Figure X-13. Portion of vegetation of subacute bacterial endocarditis showing alternating layers of fibrin and of colonies of bacteria. X 90. (WCGH, P 227 B.)

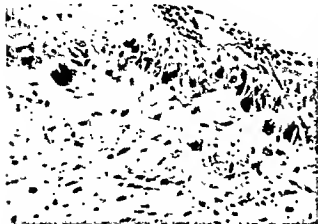


Figure X-14. Section of vegetation in subacute bacterial endocarditis. Note palisading of large histiocytic cells, many with multiple nuclei. Hematoxylin and eosin. X 250.

areas of inflammation. Often, large cells are noted with one or several round nuclei, and oval or slightly spindle-shaped cells, the long axes of the cells being directed toward the necrotic portion. Lymphocytes, histiocytes, pigment-laden phagocytes and occasional plasma cells are also evident. These cells are found within an edematous fibrillar ground substance which is traversed by many capillaries.

Early microscopic changes. While the above histologic picture is seen in advanced cases, Jaffé believed that initially there is swelling of the endothelial cells close to the line of closure. The nuclei soon disappear and the cells become necrotic. At about this time there appear, in the subendocardial layers, oval cells with vesicular nuclei, these cells often assuming palisade formations, with their long axes perpendicular to the free margins of the valves. These cells soon become necrotic and gradually fuse with the platelets of a thrombus formed in that region. The palisading of cells is characteristic (Figures X-14 and X-15) and is always demonstrable if enough sections are studied. Jaffé thought that these cells are young connective tissue cells (fibrocytes). Circumscribed, nodular, cellular infiltrations, consisting of portions of the loose edematous ground substance and a number of cells with round nuclei and much cytoplasm, are also found early. Giant cells

are often seen (Figures X-16 and X-21) particularly at the surface of these small nodules. Sometimes these giant cells resemble Langhans giant cells, with nuclei arranged at the periphery of the cytoplasm. Jaffé thought they were either fused histiocytes or fibrocytes.

Giant Cells and Necrotic Areas. Giant cells are also encountered at the marginal portion of the inflamed leaflets and within the necrotic parts of the vegetations or valves. Those at the former site seem to arise by fusion of several lining endothelial cells of the valve. Their nuclei and the nuclei of more or less intact, but swollen, endothelial lining cells are morphologically identical. It is also probably significant that they are found close to the endocardial lining. The giant cells of the necrotic foci within the vegetations generally seem to be of the foreign-body type. It has been mentioned that calcium is often deposited early within the necrotic portion of the valve or vegetation (Figures X-16, 17, 19-22). From a study of healing forms of subacute bacterial endocarditis, it appears that giant cells of foreign-body type are not rarely found adjacent to such lime deposits. Eventually necrosis occurs within the nodules described above. The necrosis starts at the periphery of the nodules and extends outside the nodules into the valvular tissue. Cocci which are usually present at the periphery do not extend into the necrotic portion of



Figure X-15. Vegetation of subacute bacterial endocarditis. Note palisading of histiocytes bordering a necrotic portion of mitral valve. Hematoxylin and eosin. X 150.



Figure X-16. Healing subacute bacterial endocarditis with acute changes still present. Note presence of giant cells, lymphocytes and histiocytic cells. The peripheral regions still show either necrosis or masses of polymorphonuclear leukocytes. Hematoxylin and eosin X 105. (Courtesy of Armed Forces Institute of Pathology, Acc. No. 37488-1.)

the nodules. Gradually evidence of suppuration appears, often with necrosis and severe destruction of the tissues. At the periphery of the necrotic areas, fibrocytes and histiocytes accumulate and these gradually extend into the necrotic portion, after which there is new formation of capillaries and attempts at healing or scarring (Figure X-18). The areas of necrosis may extend from the center of some of the nodules to the periphery, with perforation of the valvular endocardium and with formation of ulcers and thrombi.

Distinction from Acute Bacterial Endocarditis. In comparing this description with the histologic changes in valves with acute bacterial endocarditis, several important differences are evident. In acute endocarditis, exudation is much more pronounced, large areas of necrosis of the valve intermingled with polymorphonuclear leukocytes are sloughed, and large deep ulcers occur. In subacute bacterial endocarditis, ulcers are small and more superficial. Evidence of repair with newly formed connective tissue cells and actual granulation tissue is rarely seen in acute bacterial endocarditis, but is always present in subacute bacterial endocarditis. Jaffé emphasized that the formation of nodules containing giant

cells, as described above, does not occur in acute bacterial endocarditis, but is pathognomonic of subacute bacterial endocarditis. Palisading of cells is almost always encountered in subacute bacterial endocarditis. Sometimes they are also found early in acute bacterial endocarditis but here they soon become involved in the necrotizing process. Thus, from the gross description and from the microscopic details, it must be concluded that there is a type of bacterial endocarditis, called subacute bacterial endocarditis, which differs not only in its clinical manifestations, but also in some anatomic respects from acute endocarditis that is superimposed upon an old endocarditis. However, it must be pointed out at once that not all cases classified and reported as subacute bacterial endocarditis conform to the above description.

Subacute Endocarditis as a Special Entity. Libman and Friedberg (1948) repeatedly stated that acute bacterial endocarditis and subacute bacterial endocarditis are sharply distinguishable both as to their causation, and their clinical and pathologic features.

Schottmuller (1910) maintained that subacute bacterial endocarditis is an entirely separate entity, a specific disease caused by certain species of streptococci (of the Viridans group). One of the clinical characteristics of the disease is its slow protracted course. For this reason he called it endocarditis lenta ("lenta" meaning slow or insidious). Karsner (1931) stated that endo-



Figure X-17. Subacute bacterial endocarditis. Vegetation older than that shown in Figure X-15. Note superficial area of fibrin with clumps of lime salts and granulation tissue with beginning scar formation at the base. Hematoxylin and eosin. X 110.

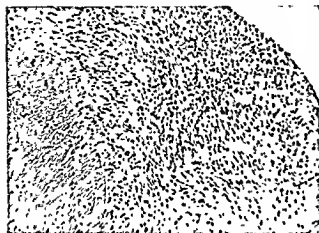


Figure X-18. Young scar tissue in healing vegetation of subacute bacterial endocarditis. Hematoxylin and eosin. X 150.

carditis lenta in its typical form is characteristic. It is not literally subacute but represents a more or less continuous formation of acute or subacute verrucous and vegetative endocarditis in close association with progressive chronic endocarditis and granulation tissue. The acute process does not ordinarily have large vegetations nor is it always free from large masses of thrombi. Pedunculated vegetations are rare. As Jaffé has shown, the microscopic picture of subacute bacterial endocarditis is characteristic.

From the clinical data, the gross, microscopic and bacteriologic findings and the relevant literature, the following facts are elicited: (1) Subacute bacterial endocarditis is a definite clinical entity, differing from acute bacterial endocarditis and uncomplicated sepsis; (2) the gross appearance of the involved valve is quite characteristic and the microscopic appearance perhaps even more characteristic; (3) *Streptococcus* sp. (Viridans group) is reported to be present in the vast majority of instances, as will be pointed out later; (4) in a high percentage of cases there is either a history of rheumatic fever or Aschoff bodies are present in the myocardium; (5) whereas it is not difficult to produce acute bacterial endocarditis experimentally, it is questionable if subacute bacterial endocarditis has ever been produced in an experimental animal.

The main gross and histologic differences between acute and subacute bacterial endocarditis

have been pointed out above. Jaffé felt certain that the histologic features were characteristic. It is also worth mentioning that several investigators have been impressed by the occurrence of hyperplasia of the reticulo-endothelial system in this disease. Istamanowa (1928) emphasized that in 30 instances of subacute endocarditis there was hyperplasia of the cells of the reticulo-endothelial system, affecting the lymph nodes, spleen, liver and bone marrow. Such hyperplasia was not present in patients with old valvular disease. However, she did not think that this reticulum cell hyperplasia differs from that seen in other infectious diseases. Jaffé was also impressed with the reticulum cell hyperplasia in subacute bacterial endocarditis.

Held and Lieberman (1943) stated that subacute bacterial endocarditis represents a state of high local and general tissue immunity to bacterial invasion. They further emphasized that the immunity resides in the local endothelial structures, as well as in the general reticulo-endothelial system. Since the reaction to this bacterial invasion is largely endothelial, they thought that the disease may rightfully be termed "infectious endotheliosis."

ROLE OF *Streptococcus* sp. (VIRIDANS GROUP)

It has often been stated that *Str. viridans* is less virulent than other streptococci and, therefore, may cause the slowly developing subacute endocarditis. Older investigators believed that particular types of green streptococci had a special affinity for the heart valves and caused subacute bacterial endocarditis.

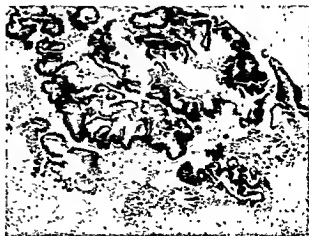


Figure X-19. Calcification of distal portion of vegetation of subacute bacterial endocarditis. Hematoxylin and eosin. X 75.

Karsner does not believe in such an elective localization. Rosebury (1944) concluded that in the majority of cases the causative organism is the gamma nonhemolytic *Streptococcus*, an alpha *Streptococcus* belonging to the Viridans group. Wheeler and Foley's (1945) studies are noteworthy. They isolated streptococci from 17 instances of subacute bacterial endocarditis and found that most of these were serologically identical and frequently belonged to the Lancefield Group D.

Wheeler and Foley also stated that the bacteriologic methods employed in the identification of alpha or "green-producing" streptococci usually indicate nothing concerning the exact identity of the strain. Interestingly enough, they emphasized that enterococci (*Str faecalis*), also occasionally encountered in subacute bacterial endocarditis are serologically identical and often belong to the Lancefield Group D. Also, Skinner and Edwards (1942) recorded 2 instances of subacute bacterial endocarditis caused by an enterococcus. Both strains were identified as members of Group D of the Lancefield classification of streptococci. (See also page 738.) From this study, one is inclined to believe that organisms of the Lancefield Group D are perhaps the ones which cause subacute bacterial endocarditis, provided other suitable conditions are present within the heart valves.

Relationship of Subacute Bacterial Endocarditis to Rheumatic Fever. Much has been written about the relationship of subacute bacterial endocarditis to rheumatic endocarditis. (See also Rheumatic Endocarditis.) Whatever this relationship may be, relevant studies have been undertaken because so often patients with subacute bacterial endocarditis give a history of one or several attacks of acute rheumatic fever. For the purpose of the following discussion, neither the clinical history of the patient, nor so-called "rheumatic stigmata," nor the histologic changes of the valves, will serve to indicate that the patient had had rheumatic fever; but instead, only the one indisputable evidence of rheumatic heart disease—the myocardial Aschoff body. From the recent literature (see MacLwaine, 1945), it becomes increasingly apparent that the more carefully the myocardium is examined in instances of



Figure X-20 (top). Dark amorphous material surrounded by a foreign-body giant cell within the myocardium. Hematoxylin and eosin. X 580.

Figure X-21 (middle). Calcific material surrounded by foreign-body giant cells. van Gieson. X 350.

Figure X-22 (lower). Foreign-body granuloma with calcium deposits in the center. Hematoxylin and eosin. X 150. These foreign-body granulomas are interpreted as evidence of healing of the subacute bacterial endocarditis.

Figures X-20 to 22 are reproduced by courtesy of Archives of Pathology from article by the author (Arch. Path., 42:574, 1946).

subacute bacterial endocarditis, the more frequently are Aschoff bodies encountered. As a matter of fact, it appears that Aschoff bodies would be demonstrable in many more hearts with subacute bacterial endocarditis if a greater number of blocks from the myocardium were examined.

In a study of sections of the myocardium of 10 children with subacute bacterial endocarditis, Saphir and Wile (1933) found Aschoff bodies in every heart. This constant finding is explained partly by the relatively larger portions of the myocardium that were studied from the hearts of children than are usually studied in adults, and partly by the interval between rheumatic fever and subacute bacterial endocarditis being usually shorter in children than in adults. Table X-9 presents data accumulated by Macellwaine to show the percentages of Aschoff bodies found in the myocardium of hearts with subacute bacterial endocarditis by various investigators. If the finding of the Aschoff body is taken as the only criterion for rheumatic heart disease, it becomes obvious that careful studies of the myocardium will indicate that a great many patients with subacute bacterial endocarditis must have had rheumatic myocarditis and, in all likelihood, also rheumatic endocarditis.

Streptococcus sp. (Viridans Group) and Rheumatic Valvulitis. At the present time, there can be no doubt of the role of the

TABLE X-9

Incidence of Aschoff Bodies Found in Subacute Bacterial Endocarditis, in Various Published Series (Macellwaine, 1945)

Authors	No. of Cases Subacute Bacterial Endocarditis	Percentage with Aschoff Bodies
Clawson and Bell (1926)	61	11.5
Gross and Fried (1937)	30	30.0
Buchbinder and Saphir (1939)	40	37.5
Saphir (1935)	35	40.0
Clawson (1929)	60	45.0
Von Glahn and Pappenheimer (1935)	26	16.0
Macellwaine (1945)	34	55.3
Saphir and Wile (1933)	10	100.0

Streptococcus sp. (Viridans group) in subacute bacterial endocarditis. The difficulty lies in explaining why the *Streptococcus sp.* (Viridans group), superimposed upon rheumatic valvulitis, produces the gross and histo-

logic picture of subacute bacterial endocarditis and the insidious clinical feature of the disease.

Some writers explain both the ensuing anatomic changes and the clinical picture on the altered reaction of the previously inflamed valve, the original infection having produced the hyperergic inflammation and the final infection causing the immune reaction, *i.e.*, subacute bacterial endocarditis. The supporters of this hypothesis assume, of course, that both diseases have a similar causative agent, the difference in the disease lying in the difference of the reaction of the host. The arguments against this attractive hypothesis are many and have been mentioned previously (see Rheumatic Endocarditis). At present this hypothesis has not been proved. The only proof for it would lie in the experimental production of both rheumatic fever and subacute bacterial endocarditis with the same organism. This requires, not only the experimental production of rheumatic endocarditis *per se*, but also the production of that most characteristic entity, an unequivocal Aschoff body. In the article by McKeown (1947), the assumption is made that Aschoff bodies have been produced experimentally. A critical review and analysis of the accompanying illustrations, however, disclose that the lesion in question, though resembling Aschoff bodies, should not be so designated. In my opinion, typical Aschoff bodies have not been produced experimentally up to the present time. It also should be emphasized that in many of the relevant experimental researches (see Rheumatic Fever) the organisms used were identified merely as *Str. viridans* and were not further classified. It may be fruitful to repeat a number of these experiments, using only the Lancefield D type and its products.

Relationship of Subacute Bacterial Endocarditis to Valvular Disease. Clawson and Bell (1926) thought that subacute bacterial endocarditis is determined by factors of virulence and resistance, and that it differs only in degree from other forms of endocarditis. On the other hand, Von Glahn and Pappenheimer (1935) concluded that subacute bacterial endocarditis is a new infection superimposed on an unhealed rheumatic endocarditis. Other possibilities have been suggested why *Streptococcus sp.* (Viridans group) produces the histologic picture of subacute bacterial endocarditis if engrafted upon a rheumatic valvulitis. Saphir and Wile (1933) emphasized that the finding of typical Aschoff bodies in the

myocardium in cases of subacute bacterial endocarditis is not an immune response in a previously hypersensitive patient. They maintained that it would be difficult to explain the simultaneous response of a tissue in two different ways, i.e., exhibition of both a hypersensitive reaction represented by the Aschoff body, and an immune reaction represented by the vegetation of endocarditis. They stated that the rheumatic valvulitis somehow facilitates subsequent localization of bacteria. Gross and Fried (1937) believed that some of the cases of acute and subacute bacterial endocarditis were "thrown into activity" by the superimposed bacterial infection, rather than that the activity of the rheumatic process predisposed to the bacterial endocarditis. MacIlwaine (1947) believed that the acute changes seen in rheumatic endocarditis are such as to offer a focus for the localization of bacteria from the circulating blood. In subacute bacterial endocarditis the organisms are relatively avirulent and require for their implantation some localizing factor in the valves themselves. It is suggested that such a factor is the presence of rheumatic lesions and that these are the determining pathogenic factors in the majority of cases of subacute bacterial endocarditis.

Postulates for Specific Criteria of Subacute Bacterial Endocarditis. Three facts appear to stand out: (1) The clinical picture in subacute bacterial endocarditis is characteristic; (2) a more or less specific organism, a *Streptococcus* belonging to the Viridans group, is the offending organism, and (3) if carefully sought, Aschoff bodies, the only definite histologic criterion of rheumatic heart disease, are often found in the myocardium. The question must be raised immediately whether the last 2 factors will be found regularly in carefully studied cases. Perhaps it may be going to extremes of precision to recommend, according to our present knowledge, that subacute bacterial endocarditis be diagnosed anatomically, not only on the basis of the fairly characteristic gross and histologic picture of the valves, but also, if evidence of rheumatic endocarditis is brought forward, by the detection of Aschoff bodies. Bacteriologically, a *Streptococcus* belonging to the Viridans group should be demonstrated. If these criteria are established, subacute bacterial endocarditis will become a much more precise entity, not only clinically, but also bacteriologically and pathologically.

The objections to such strict criteria are obvious. Cases are on record of subacute bacterial endocarditis in which organisms other than strep-

tococci were demonstrable. Besides, there are many reports of subacute bacterial endocarditis engrafted upon congenital defects in the heart and upon syphilitic aortic valves. There are also many instances of acute bacterial (streptococcal) endocarditis which are superimposed on old inflammatory valvular lesions. These definitely are not instances of subacute bacterial endocarditis, and yet the old inflammation of the valve is often assumed to be of rheumatic origin. Subacute bacterial endocarditis caused by organisms other than those belonging to the Viridans group are comparatively rare. Cases of this type should always be re-studied carefully bacteriologically to see if, in addition to the bacterium first discovered, another might also be present. MacLean and Howell (1947) showed that, in a case of subacute bacterial endocarditis, 2 types of streptococci were present, one of which had become sensitive to penicillin. As previously mentioned, Wheeler and Foley (1945) demonstrated that certain enterococci which were encountered in subacute bacterial endocarditis were serologically identical and often belonged to Lancefield Group D, that a gross anatomic diagnosis of subacute bacterial endocarditis alone is often insufficient, and that a careful microscopic examination of the valvular lesions is essential to verify the diagnosis. In many reports, the diagnosis has been made only on the basis of the clinical or of the clinical and gross anatomic findings, and has not been supplemented by microscopic studies. The same criticism may be made of many reports of subacute bacterial endocarditis engrafted on either congenital cardiac defects or syphilitic aortic valves. In most of these instances, the diagnosis had been made principally on the findings of a *Streptococcus* of the Viridans group. In retrospect, many of these cases seem to be instances of acute bacterial endocarditis engrafted upon old valvular defects. Again, it must be emphasized that the mere demonstration of a *Streptococcus* of the Viridans group is not sufficient to make a diagnosis of subacute bacterial endocarditis.

Koletsky's (1942) observations lend no support to the belief that syphilis is a significant predisposing factor in the development of subacute bacterial endocarditis. He studied 5 cases of combined syphilitic heart disease and bacterial endocarditis among 4000 consecutive autopsies. In 2 there was syphilitic aortitis alone and in 3 there was involvement of the aortic valve. He did not believe that any significance could be attached to the syphilitic lesion as a precursor of



Figure X-23. Healing vegetations in subacute bacterial endocarditis of mitral valve, following treatment with penicillin. (WCGH, 50 A 29.)

the endocarditis, since stigmata of rheumatic fever were demonstrated in 4 cases, and in at least 2 of these there were syphilitic and rheumatic lesions of the aortic valve. In the fifth case, syphilis was confined to the root of the aorta and an acute bacterial endocarditis was apparently imposed upon a normal aortic valve.

Acute Bacterial Endocarditis and Old Endocarditis. Cases are also on record of acute bacterial endocarditis caused by streptococci, superimposed on old valvular lesions which were interpreted to be of rheumatic origin. Neither the clinical picture nor the gross picture was characteristic of subacute bacterial endocarditis. It must again be emphasized that acute bacterial endocarditis, which for some reason is not severe enough to cause death, may heal with scarring of the valve. As a matter of fact, there is no reason whatever, as will be discussed later, why an old mitral or aortic endocarditis must always be labelled old "rheumatic endocarditis" rather than old "nonspecific" endocarditis. It seems obvious that acute bacterial endocarditis may undergo healing and that such a nonspecific inflammatory process eventually will come to a standstill. The result will be

a deformity of the valve. Thus, if there are no definite indications that such old valvular lesions are rheumatic in origin, a rheumatic etiology should not be assumed. Such an instance of acute and old endocarditis should be classified as acute bacterial (*Streptococcus* sp., Viridans group) endocarditis superimposed on an old (nonspecific) endocarditis and not as subacute bacterial endocarditis, simply because of the findings of *Streptococcus* of the Viridans group, recent vegetations and an old endocarditis. Furthermore, every case of bacterial endocarditis caused by any type of organism, superimposed upon a rheumatic endocarditis, should not be accepted positively as subacute bacterial endocarditis.

Nomeoclature. It is perfectly clear that "subacute bacterial endocarditis" is not a correct term, since the disease is not just a subacute inflammation. There are a number of other terms used for subacute bacterial endocarditis, such as malignant endocarditis, chronic infectious or chronic septic endocarditis, and endocarditis lenta. Schottmüller (1910) used the term "endocarditis lenta" and thought that this was a specific disease caused

by *Str. viridans*. Libman and Friedberg objected to this term because they believed subacute bacterial endocarditis might be caused by various organisms and not by *Str. viridans* alone. Karsner (1931) favored the term endocarditis lenta, meaning slow endocarditis, which expresses both the clinical course and the anatomic nature of the disease. In view of the above concepts, it is evident that the term "subacute bacterial endocarditis" is misleading.

Histologic Changes as Result of Antibacterial Treatment (Penicillin). Most of the histologic studies of the appearance of the valvular lesions following treatment with penicillin (Figure X-23 to 25) are based on a comparison between changes of the valves as described in the literature in untreated patients or as observed in untreated control cases, and changes encountered in the valves of treated cases.

Karsner and Lund (1948) stated, however, that this is not a precise evaluation, that interpretation of changes following penicillin therapy is difficult because of occurrence of variable degrees of fibrosis and fibrin formation in untreated cases. Moore (1946) stated that administration of penicillin in subacute bacterial endocarditis promotes healing but that the basic processes of healing are not modified.

These processes include the following: covering of the exposed surface of the vegetation with fibrous tissue, invasion of the layer of colonies of bacteria, phagocytosis of bacteria, calcification of bacterial colonies, hyalinization and calcification of the central core of

the vegetation and endothelialization of the spaces and clefts in the vegetation. Moore believed that in some patients healing is accompanied by excessive calcification and that the result may be calcific stenosis of the valve.

Carnes and Tinsley (1946) described grossly small calcified nodules, small flat granular vegetations, fibrous thickenings and fusion between cusps. In 2 of their 5 cases which they classified as showing evidence of healing, perforations of the cusps were noted. No mention was made as to whether the perforation occurred in a healing cusp, or was located where ulcerative and vegetative endocarditis was still present. In the microscopic examination, they were impressed with a few focal areas of leukocytic infiltrations and with calcific nodules that still contained gram-positive cocci. Also encountered were basophilic nuclear debris and an infiltration of mononuclear and multinuclear cells. Two other instances, seemingly presenting more advanced healing, disclosed a relatively acellular connective tissue in which large masses of coarse calcific material were embedded but in which no bacteria, necrosis or leukocytic infiltrations were seen. Hildebrand and Priest (1947) reported 34 instances of penicillin-treated subacute bacterial endocarditis. The lesions at autopsy were small and firm, and calcification sometimes was marked. Healed valvular lesions resembled healed stages of rheumatic valvulitis. Polymorphonuclears were frequently noted and fibrin seemed to persist. Geiger and Durlacher (1947) found pale, dark and smoothly-endothelialized masses of connective tissues and areas of calcification, but no bacteria.

The histologic criteria of healing are given in Table X-10.

TABLE X-10
Histologic Criteria of Healing in Subacute Bacterial Endocarditis,
According to Jones and Associates (1947)

Stage 1. Indistinguishable from vegetations of untreated cases; active inflammation.			
Stage 2. Much organization, slight or no inflammatory reaction, intermediate between stages 1 and 3.			
Stage 3. Organization advanced; lesion probably nearly healed.			
Feature	Stage 1	Stage 2	Stage 3
Polymorphonuclear leukocytes in vegetation or valve	Moderate number	Few or none	None
Mononuclear cells in vegetation	Some	Some	Few or none
Growth of endothelial cells over vegetation	Never	Never	Often
Newly formed fibrous tissue	Little	Much, cellular	Variable amount
Organisms	Yes	Yes	Sometimes
Positive culture from vegetation	Sometimes	Never	Never



Figure X-24. Aneurysm of anterior leaflet of mitral valve following treatment of subacute bacterial endocarditis with penicillin. (WCGH, 45 A 429)

Jones and associates (1947) pointed out that in untreated bacterial endocarditis, although acute inflammatory changes are always present in some part of the lesion, there may also be areas of healing. In assessing healing in these cases, it is necessary to examine several sections from each vegetation and to form an opinion for the composite picture. Angrst and Marquiss (1954) described distorted valves with healed perforation and sometimes calcific vegetation.

There are other evidences of healing of subacute bacterial endocarditis. Saphir and Leroy (1948) reported *true aneurysms* of the mitral valve (Figures X-23, 24 and 25). These aneurysms are outpouchings of portions of valves, in the absence of vegetations or ulcerations. Grossly these aneurysms superficially resembled broad-based, healed vegetations covered by the endocardium, but on touch they collapsed. They were obviously the result of a circumscribed valvulitis with consequent formation of granulation tissue and young scar tissue which, because of intracardiac pressure, formed saccular outpouchings. All these aneurysms were covered by valvular endothelium.

Cames and Tinsley (1946) also mentioned

aneurysms in their studies of healing bacterial endocarditis but did not state whether the aneurysms were mycotic (false aneurysms) or true aneurysms of the type reported by Saphir and Leroy. It has been emphasized repeatedly that *calcification* within the vegetation is regarded as evidence of healing. Saphir (1946) found small calcific emboli in the myocardium of patients with subacute bacterial endocarditis (Figures X-20 to 22). These patients had been treated with sulfonamide compounds and penicillin and their hearts presented healing vegetations of the aortic valves. Such calcific emboli had caused typical foreign-body granulomata within the myocardium. It was emphasized that granulation tissue occurs at the base of the vegetation while calcium is deposited at the periphery of the vegetation within the necrotic masses. Obviously such calcium particles can break off easily and may lodge in branches of coronary arteries, causing foreign-body granulomata. These findings were regarded as characteristic evidences of healing of subacute bacterial endocarditis. As has been stated previously, calcification of vegetation also occurs and has been observed in untreated instances of acute and subacute bacterial endocarditis. Cullinan and Baxter (1930) reported an instance of pneumococcal endocarditis in which they stressed the great rapidity (23 days) with which calcification took place in newly formed vegetations. It is interesting that there were also calcareous emboli in the kidneys.

COMPLICATIONS AND SEQUELAE OF ACUTE AND SUBACUTE BACTERIAL ENDOCARDITIS

The sequelae of acute and subacute bacterial endocarditis may be grouped according to the occurrence of septicemia, embolism to organs other than the heart, and embolism and other changes within the heart itself. The last will be discussed first.

Mural Endocarditis. Mural endocarditis occurring as a complication of valvular endocarditis has been discussed previously. Also the occurrence and mechanisms of *erosive mycotic aneurysms* have been described. Levy and Hull (1947) reported such an apparently true aneurysm which was healing, situated in the interventricular septum. It had perforated into the right ventricle.

Myocardial Changes in Bacterial Endocarditis. Various *degenerative changes* in the



Figure X-25. Aneurysm of aortic cusp representing healed subacute bacterial endocarditis following treatment with penicillin, in heart with old rheumatic aortic and mitral valvulitis. (WCCG, 50 P 62.)

myocardium, resulting from the underlying acute infectious disease, have been described; among these are cloudy swelling and fatty degeneration. Grossly, the myocardium is almost invariably softer than normal, its cut surface having a cooked appearance, and its architecture being obscured. In addition to these degenerative changes, one often observes gray or yellow streaks in the myocardium, which are clearly seen through the intact endocardium. On section of the myocardium, there are also encountered occasional red foci of minute hemorrhages and yellow areas surrounded by hemorrhagic zones. The gross appearance of the myocardium in these instances does not indicate the type of changes that may be encountered upon microscopic examination. In studying a series of hearts by means of multiple sections cut from many blocks, it becomes obvious that there is practically no instance of acute bacterial endocarditis which does not show one or more of the various changes which will be discussed presently. Table X-11 lists the pertinent changes encountered in the myocardium in 35 instances of subacute bacterial endocarditis (Saphir, 1935). Petechial hemorrhages were found 6 times microscopically, were very recent and were in no way

related to embolic phenomena. Circumscribed acute inflammatory changes with foci of necrosis and abscesses were found 15 times. Accumulations of polymorphonuclear leukocytes were usually present in perivascular areas and often extended into the interstitial tissue between the heart muscle fibers. Small foci of necrosis in individual muscle fibers were often noted. The necrotic centers were infiltrated and surrounded by many polymorphonuclear leukocytes, and here and there clumps of bacteria were present in the center of the necrosis. Outspoken abscesses were usually located just beneath the pericardium

TABLE X-11

Summary of Microscopic Myocardial Changes Found in 35 Cases of Subacute Bacterial Endocarditis (Saphir, 1935)

Type of Lesion	Number of Cases
Petechial hemorrhages	6
Acute myocarditis	15
Foci of necrosis and abscesses	15
Minute infarcts	
Recent	2
Organized	28
Healed	13
Emboli	18
Perivascular, subacute and chronic inflammation	11
Aschoff bodies	14
Perivascular fibrosis	15



Figure X-26. Small myocardial infarct in subacute bacterial endocarditis. Note interruption of muscle fibers by cellular scar tissue. Hematoxylin and eosin. X 175.

and also beneath the endocardium of the left ventricle. These are more common in acute than in subacute bacterial endocarditis. *Acute myocarditis* was encountered 15 times among the 35 instances. This myocarditis was diffuse and consisted of infiltrations mainly of polymorphonuclear leukocytes.

Clawson (1928) found associated *myocarditis* in 24 per cent of his cases of endocarditis *lenta* and in 24.5 per cent of his cases of acute bacterial endocarditis. Yet he emphasized that, while myocarditis is practically always associated with rheumatic endocarditis, it seldom occurs in the bacterial form. *Perivascular infiltrations* were encountered in 11 hearts, the predominating type of cell being the lymphocyte. Only occasionally a few plasma cells and endothelial leukocytes were also found. These infiltrations were well confined to the perivascular areas and did not extend into the adjacent parenchyma. Multinucleated cells or other cells resembling those seen in Aschoff bodies were not observed in these fields, and the cellular elements showed no particular arrangement. *Perivascular areas of fibrosis* were also often encountered, in which occasionally a few inflammatory cells were present. These areas of perivascular fibrosis were obviously old scars, but whether the original lesion was an Aschoff body or a nonspecific perivascular infiltration could not be determined. In 14 instances, outspoken *Aschoff bodies* were encountered. The findings of Aschoff bodies, the characteristic myocardial nodules of acute rheumatic

fever, and their relation to subacute bacterial endocarditis has been discussed previously. The most commonly encountered lesions were *minute infarcts* (Figure X-26). In subacute bacterial endocarditis these infarcts are often present in the organizing stage.

Many spindle-shaped cells were found replacing heart muscle fibers. A few lymphocytes and occasional polymorphonuclear leukocytes were scattered among these cells. Often phagocytic cells were encountered, their cytoplasm filled with blood pigment. Often, too, newly formed blood vessels were present in these lesions. Recent infarcts were also occasionally encountered, infiltrated and bordered by polymorphonuclear leukocytes and a few red blood cells. Seabury (1947) emphasized that recent or old myocardial infarcts or both were found in 25 per cent of the cases in which autopsies were performed. White (1951), in stating that cardiac infarcts are very rare in subacute bacterial endocarditis, probably only referred to large infarcts recognizable grossly. Schlesinger and Reimer (1955) described foci of myocytolysis which differed from minute infarcts in that the stroma was not involved.

From this description, it is clear that the myocardium may show varying changes. The infarcts are easily explained by the presence of minute emboli (Figure X-27), obviously arising from the vegetations. Larger emboli, blocking the mouths of the coronary arteries or the larger branches, are relatively infrequent. (In only one of the 35 instances reported by Saphir [1935] could an embolus be demonstrated in a larger branch of the coronary artery.) Emboli in the small intra-myocardial branches (Figure X-27) obviously would be more commonly reported if one looked for them. Minute foci of polymorphonuclear leukocytic infiltrations and minute abscesses are probably the result of the lodging of bacteria in the smallest branches of the coronary arteries.

"Bracht-Wächter Bodies." Throughout the literature, the term "Bracht-Wächter bodies" is often used, denoting circumscribed inflammatory lesions in the myocardium, characteristic of, but not specific for, subacute bacterial endocarditis. It is remarkable that this term is so often applied, even by those not concerned with the microscopic study of such lesions, in spite of the fact that there is no

clear-cut entity which could possibly be assigned such a term. Thus, Perry (1936) stated that Bracht-Wächter bodies are cellular foci in the myocardium consisting, in early stages, of an almost equal number of polymorphonuclear leukocytes and lymphocytes. Libman and Friedberg (1948) emphasized that they replace the muscles and are not lesions of the interstitial tissue, while White (1951) described them as areas of mononuclear cell infiltrations of the interstitial tissue. The variation in the description of the so-called "specific lesions" of the myocardium in subacute bacterial endocarditis can easily be explained by the fact that Bracht and Wachter never described a single entity. Because of the existing misconception of what a Bracht-Wachter body is, it may be of interest to review their original study in more detail.

Bracht and Wächter (1909) did not study hearts with subacute bacterial endocarditis. Shortly after Aschoff's discovery of the specific nodule in the myocardium in acute rheumatic endocarditis, they tried to determine if an Aschoff body could be produced experimentally in rabbits. Blood cultures, taken from 2 hearts in which Aschoff bodies had been found, disclosed diplo-streptococci resembling a *Streptococcus* of the Viridans group. These streptococci were injected into 2 rabbits. Into a third rabbit were then injected streptococci which had been obtained from the heart-blood of the original 2 rabbits after their death. For control experiments, Bracht and Wachter used 3 rabbits. Two of these were given intravenous injections of streptococci obtained from a paronychia, and the third, streptococci isolated from infected tonsils. Thus, Bracht and Wachter used only 6 rabbits for their experiments; 3 for the actual experiment and 3 as controls. In 2 rabbits, following the intravenous injections of streptococci isolated from the blood of a patient with acute rheumatic endocarditis, the myocardium disclosed small areas of necrosis, surrounded by lymphocytes and fibroblasts, with an occasional giant cell; cellular infiltrations in the interstitial tissue, occasionally involving the heart muscle fibers; accumulations of lymphocytes and isolated plasma cells. The third rabbit was given an intravenous injection of blood obtained from the hearts of the first 2 rabbits, and was killed 16 days later; its myocardium showed scars replacing muscle fibers and

some calcification. In the myocardium of the 3 control rabbits only areas of necrosis were found, surrounded by many polymorphonuclear leukocytes. No normal rabbits were used as control animals.

From this short review it should be clear that (1) Bracht and Wachter never studied the myocardium of subacute bacterial endocarditis microscopically; and (2) in their 3 experimental and 3 control rabbits, no single characteristic lesion was encountered in the myocardium. It is hard to understand how the term "Bracht-Wächter body" has been able to persist in the literature. It would, therefore, seem wise to discard this term and instead use descriptive terms for the various lesions encountered in the myocardium.

Pericarditis. Pericarditis is rarely found associated with subacute bacterial endocarditis but is somewhat more frequent in acute bacterial endocarditis. In such instances there are usually small abscesses or infected infarcts in the myocardium close to the pericardium, and the pericarditis is fibrinopurulent in nature. A fresh fibrinous pericarditis may be the result of a concomitant rheumatic infection, of uremia or of an intercurrent pneumonia, with acute pleuritis. A mycotic aneurysm may perforate into the pericardium, producing at first acute fibrinopurulent pericarditis and, later, hemopericardium (see page 697). Among 50 cases of subacute bacterial endocarditis, Demman (1942) encountered 13 with pericarditis.



Figure X-27. Organizing embolus in a small coronary artery in subacute bacterial endocarditis. Hematoxylin and eosin. X 175.



Figure X-28. Focal necrosis of kidney glomerulus in subacute bacterial endocarditis. Hematoxylin and eosin. X 325.

Embolism and Infarction. Gross embolism of the coronary arteries is infrequent. However, of all emboli within the large branches of the coronary arteries or at their mouths, the most commonly encountered are those arising from a vegetation of the aortic valve. Large emboli may cause unexpected death. Also, large vegetations of the aortic valve, soft enough so that they can be moved easily by the blood stream without breaking off, may suddenly impinge upon the mouth of one of the coronary arteries. This is more likely to happen when there is also severe ulceration with rupture of either the right or left aortic cusp. Multiple small emboli within the small intramyocardial branches of the coronary arteries are extremely common. These and the resulting minute infarcts, which have been regarded as the most characteristic single myocardial lesion, have just been discussed. Embolism and resulting infarcts are common in the spleen, kidneys and the brain. If the spleen is the seat of an infarct, it may actually rupture. Kennedy and Seed (1947) collected 10 such instances from the literature, and reported 1 additional observation. Rupture usually occurs in a spleen that is the seat of an infected infarct or of a frank abscess. Perisplenitis, the result of an infarct, is common. Although infarcts in the kidneys as well as in the spleen are more likely to be infected in acute bacterial endocarditis

and to be bland in subacute bacterial endocarditis, it is not rare to find infected infarcts in the latter. The incidence of infarction in the spleen, kidneys and brain in a series of 44 cases of acute bacterial endocarditis and of 87 cases of subacute bacterial endocarditis as encountered by Buday, is given in Table X-12.

TABLE X-12

Incidence of Infarction in Bacterial Endocarditis (Buday, 1929)

Disease	No. of Cases	Spleen	Kidneys	Brain	In Various Organs Per Cent
Acute bacterial endocarditis	44	7	10	not given	45
Subacute bacterial endocarditis	87	25	45	23	76

Buday (1929) found infarcts in various organs in acute bacterial endocarditis in 45 per cent and in subacute bacterial endocarditis in 76 per cent. Among Denman's 50 cases of subacute bacterial endocarditis, infarcts in the spleen were found 27 times and in the kidneys 17 times. Emboli are also often found within the cerebral arteries and in the arteries of the extremities. In Buday's series emboli were found 23 times in the intracranial arteries, as follows: internal carotid artery, once; middle cerebral arteries, 20 times; and basilar artery, twice. Intestines and lungs are not often involved. Mycotic embolic aneurysms are not unusual, all such aneurysms being erosive in nature (see page 715). Such an aneurysm may involve any artery; the artery may then rupture with resulting hemorrhage, the hemorrhage in some cases being fatal. Erosive aneurysms may also be the result of bacterial invasion directly from the blood stream without the intervention of an infected embolus.

Pirani (1943) stated that in subacute bacterial endocarditis the inflammatory process of the aortic, and rarely of the tricuspid and mitral valves, may extend into the subjacent myocardium of the interventricular septum, or into the membranous septum. In contrast to the occurrence of this complication in acute bacterial endocarditis, lesions of this type in subacute bacterial endocarditis according to Libman (1913), almost never cause ventricular perforation. However, such an instance was described by Levy and Hull (1947). Arteritis alone may be caused by the circulating bacteria. In subacute bacterial endocarditis, arteritis of minute arteries and inflammation of capillaries, as Libman and Fried-

berg (1948) stated, are sometimes presumed to be toxic, or possibly allergic lesions, inasmuch as bacteria may be absent.

Bernard and associates (1957) have reported rupture of the heart following infarction in subacute bacterial endocarditis.

Various cutaneous lesions, such as the Osler nodes (see below), are now believed to be the result of inflammation of the walls of the small vessels, associated with endothelial hyperplasia and obliteration of lumina. Focal glomerulonephritis (Lohlein's nephritis) of focal embolic glomerulonephritis (Figure X-28), often referred to as "flea-bitten" kidney, is common in subacute bacterial endocarditis. Baehr (1931) reported microscopically typical healed embolic glomerular lesions in the kidneys of 34 of 57 patients with subacute bacterial endocarditis in the bacteria-free stage of the disease. Bell (1932) found diffuse glomerulitis in 65 per cent of patients with subacute bacterial endocarditis, and embolic or focal glomerulitis in 53 per cent. He described 2 distinct types of embolic lesions, the fresh hyaline lesion, which is a capillary thrombus with necrosis of the capillaries resulting from the lodgement of bacteria, and the fibrous lesion which is characterized by a marked growth of the basement membrane of the capillaries. Bell found diffuse glomerulitis in acute primary bacterial endocarditis in 29 per cent and in secondary acute endocarditis in 33 per cent. Libman and Friedberg (1948) in quoting observations by Baehr, stated that focal embolic glomerulonephritis is almost specific for subacute bacterial endocarditis. They also pointed out that the glomerular lesion is usually produced by emboli but it is probable that local vascular inflammation and closure play a contributory, if not dominant, role in its production. The end result of such lesions is a characteristic wedge-shaped or pyramidal scar within the subcapsular space of the glomerulus.

Septicemia. Because of the underlying septicemia, changes which are usually found in uncomplicated septicemias are also encountered here. Thus, cloudy swelling and fatty changes of the parenchymatous organs

are common. Splenic hyperplasia, sometimes of severe degree (weight of spleen, up to 800 Gm.), is always encountered. Because of the heart failure, which is not rare in subacute bacterial endocarditis, combinations of cloudy swelling, fatty degeneration or splenic hyperplasia with morphologic evidence of passive hyperemia in these organs may be met. Because of the septicemia, *encephalitis* is not a rare complication; in Kimmelstiel's (1928) experience, *encephalitis* was more often encountered than larger cerebral hemorrhages or *encephalomalacia*, as a result of emboli or embolic mycotic aneurysms.

Among the skin lesions, *petechiae*, Osler's nodes and Janeway lesions are usually mentioned. *Petechiae* are common. They may occur with or without white or yellow-white centers. In the skin they may be absent, or few or numerous. Sometimes they are seen best in the conjunctivae. They may be either the result of embolism (although bacteria are usually not found in these lesions), the result of local inflammatory vascular lesions, or of a nonspecific proliferation of endothelial cells lining the capillaries. They are not pathognomonic of either acute or subacute bacterial endocarditis.

Osler's Nodes. Osler's nodes are observed in about 50 per cent of cases of subacute bacterial endocarditis. They are small, raised, red lesions about the size of a pea. They occur commonly on the fingertips, under the nails, and on the soles of the feet, and more often on the upper than on the lower extremities. These cutaneous nodes are probably, as mentioned before, the result of local, possibly toxic or allergic inflammatory changes in the wall of the blood vessels. These culminate in a proliferation of endothelial cells, with final occlusion of the lumina. Thus, the center of the node is often the seat of necrosis and is surrounded by a perivascular infiltration, mainly of polymorphonuclear leukocytes.

Janeway Lesions. Janeway (1899) gave the following description to the lesions which bear his name: "I have noted numerous small hemorrhages with slight nodular character in the palms of the hands and in the soles of the feet,



Figure X-29. Subacute bacterial endocarditis of aortic valve, superimposed on old endocarditis both of rheumatic and syphilitic types. Note syphilitic aortitis, extension of bacterial vegetations to aorta, and formation of mycotic aneurysm involving a sinus of the aortic valve. (WCCB, 40 A 412.)

when possibly the arms and legs had but a scanty crop in malignant endocarditis; whereas this has not been my experience with the processes likely to be mistaken for it." They are usually described as small, often hemorrhagic lesions, measuring 1 to 4 mm. in diameter, which may appear as macules or papules.

Myocardial Failure. Although modern treatment with penicillin is relatively recent, there are a number of cases on record of patients who ostensibly had been cured of bacterial endocarditis, but subsequently died of myocardial failure. This myocardial failure is explained by progressive healing of the inflammation of the valvular lesions with subsequent progressive disturbances in function.

Thus, Rosenblatt and Loewe (1945) believed that death in 2 of their patients was caused by cardiac failure incident to aortic valvular insufficiency. Carnes and Tinsley (1940) concluded that their patients died in cardiac failure which was primarily the result of the extreme valvular damage. On the other hand, Hildebrand and Priest (1947) attributed the cause of death in

their patients to extensive myocardial lesions. Jones and associates (1947) also stated that cardiac damage caused by the infection is the chief cause of failure. Fiese (1947) emphasized that cardiac failure is common in subacute bacterial endocarditis. Eighty per cent of 40 untreated patients had evidence of cardiac failure at autopsy. He stated that cardiac failure, after otherwise successful treatment, depends on various factors; the most important are the previous heart reserve, the size of the heart, the patient's age, the type of cardiac lesion, and the height of the fever.

In the older literature it was usually stated that patients with rheumatic endocarditis eventually succumb to heart failure, while patients with subacute bacterial endocarditis die of the infection. This statement is obviously not true. If the myocardium is studied carefully by means of many microscopic sections, it is remarkable how many changes one encounters. In a study of 40 patients who died with subacute bacterial endocarditis before the era of modern treatment, Buchbinder and Saphir (1939) found that 18 of these, or 45 per cent, clinically revealed evidences of heart failure and, at necropsy, severe chronic passive hyperemia. The frequency of heart failure, as elicited clinically and as verified at autopsy, was 75 per cent. Since the infection is amenable to cure and since the acute and subacute valve lesions may heal, it seems evident that a patient who survives the infection may gradually develop disturbances in function of the valves with resulting hypertrophy of the heart and, thus, subsequently succumb to heart failure. This is particularly so because of the severe widespread damage to the heart muscle, which had occurred in the more acute stages. It is easy to understand that the multiple small infarcts within the myocardium, which have been discussed before, produce permanent damage to the myocardium. Necrotic muscle fibers in the heart do not regenerate, but are replaced by scar tissue. On the other hand, it is conceivable that the myocarditis, particularly if it involves principally the interstitial tissue, may occasionally subside without permanently damaging the heart. Modern treatment is designed to combat the infection, but cannot possibly have any effect upon the established infarcts, since necrosis of muscle fibers and subsequent organization and scar formation are irreversible processes. Thus, patients with subacute bacterial endocarditis despite treatment, may still have multiple small infarcts in their myocardium. Since infarcts are usually small,

they may not present clinical evidence of myocardial damage. Likewise, an infection that consists principally of an interstitial acute myocarditis may remain clinically silent. However, if a patient with such a myocardial lesion should subsequently develop any disease, even if it be trivial, which produces an additional strain on the heart, and particularly if he should develop myocarditis or recurrence of the endocarditis with myocardial damage or coronary sclerosis, his myocardium may gradually fail.

Causes of Death in Acute and Subacute Bacterial Endocarditis. Patients with bacterial endocarditis may die as a result of severe *septicemia*. They may succumb as the result of *embolic phenomena*, particularly of emboli in the cerebral arteries with resulting encephalomalacia and cerebral hemorrhage. They may develop large coronary emboli. *Mycotic aneurysms* may develop and death may result from a rupture of the involved blood vessel. Complicating *nephritis* may cause death. If such a nephritis is of the so-called embolic type, patients usually do not show evidence of uremia. However, if the nephritis is diffuse, death in uremia may ensue.

Libman and Friedberg mentioned that death may be caused by a large vegetation acting like a ball-valve thrombus and occluding the orifice of a valve. Kidd (1935) mentioned unsuspected death in bacterial endocarditis as the result of myocardial aneurysm of the conduction system. Unexpected death was reported by Munck (1946) in 18 patients with valvular disease; 1 patient had an acute and 2 patients, subacute bacterial endocarditis. Montz and Zamcheck (1946) also reported instances of unexpected death.

Although little attention has been paid to morphologic and clinical evidence of myocardial damage, from the foregoing it is clear that a number of patients succumb from *myocardial failure* as a result of the following three conditions: (1) multiple infarcts of the heart, (2) acute myocarditis and (3) progressive valvular impairment.

carditis may be engrafted upon valves which are deformed, as the result of an old endocarditis (Figure X-29), of a congenital anomaly or, in the case of the aortic valve, of syphilis.

Bacterial Endocarditis Superimposed on Old Endocarditis. Such an old endocarditis is the result of a rheumatic endocarditis, or of a nonspecific endocarditis. The old inflammation might have produced either an insufficiency of the valve or a stenosis of its orifice. In the presence of severe stenosis of its orifice, the mitral valve is rarely the seat of subsequent bacterial endocarditis. Often so-called bicuspid aortic valves, usually the result of an old endocarditis, and calcareous aortic valves, may be the seat of bacterial endocarditis. Reference to the coincidental occurrence of recent and old endocarditis has been made previously.

Koletsky (1943) reported that among 50 hearts with bicuspid aortic valves, he found superimposed bacterial endocarditis in 8. In 4 the bacterial disease was acute and in 4 subacute. A careful histologic analysis disclosed that 7 of the bicuspid aortic valves were deformed as a result of acquired lesions, and only 1 was of congenital origin. He pointed out that every one of these hearts showed definite stigmata of rheumatic fever.

Bacterial Endocarditis Superimposed on Congenital Heart Disease. Abbott (1926) emphasized that acute and subacute bacterial endocarditis were serious complications of cardiac anomalies.

Of 555 hearts with congenital anomalies, 98 (17.6 per cent) presented an endocarditis. Of these, 40 per cent were defects of the base of the interventricular septum. Brown (1939) pointed out that the risk of infective endocarditis is definitely greatest in the so-called cyanotic group of patients. He stated that the greatest frequency of infective endocarditis is found associated with patent ductus arteriosus and bicuspid aortic valve.

Vegetations do not necessarily develop just at the site of the anomalies but rather at the site of the intracardiac trauma (see page 728). This is particularly borne out in defects of the membranous portion of the interven-

BACTERIAL ENDOCARDITIS SUPERIMPOSED ON PRE-EXISTING VALVULAR DEFORMITIES

As has been stated before, bacterial endo-

TABLE X-13

Frequency of Bacterial Endocarditis in Various Congenital Anomalies,* in Patients Under and Over Two Years of Age (Gelfman and Levine, 1942)

Type of Defect	Total			Number of		
	Number of Patients, All Ages	Instances of Bacterial Endocarditis	Percentage	Patients over Two Years Old	Instances of Bacterial Endocarditis	Percentage
Interatrial septal defects	179	0	0	45	0	0
Interventricular septal defects	164	17	10.4	31	13	41.9
Patent ductus arteriosus	134	4	3.0	14	4	28.0
Congenital bicuspid aortic valve	63	11	17.4	52	11	21.2
Congenital pulmonic stenosis	43	8	18.6	17	5	29.4
Coarctation of aorta	33	1	3.0	10	1	10.0
Congenital bicuspid pulmonic valve	21	0	0	9	0	0
Congenital pulmonary atresia	15	0	0	2	0	0
Cor trioculare batriatum	13	1	7.7	2	1	50.0
Congenital aortic stenosis	11	0	0	3	0	0
Congenital tricuspid stenosis	9	0	0	1	0	0
Congenital mitral stenosis	7	0	0	3	0	0
Congenital subaortic stenosis	2	1	50.0	2	1	50.0
Maladie de Roger, uncomplicated	44	10	22.7	14	8	57.1
Tetralogy of Fallot	10	2	12.5	7	2	28.6

* No case was listed if the single defect was either (1) a patent foramen ovale in a patient under one year of age unless it was 1 cm. or more in diameter, and completely or partially undefended to allow true admixture of venous and arterial blood, (2) a patent ductus arteriosus before the first postnatal month, unless the patency was abnormally wide; (3) an anomaly of the coronary arteries, the aorta or its branches, the pulmonary arteries, or the great veins, or (4) fenestration of the semilunar cusps.

tricular septum, in which condition the vegetations are located on the septal leaflet of the tricuspid valve, since this leaflet is exposed to trauma by the blood stream flowing from the left to the right ventricle.

Furlong (1941) listed the cardiac anomalies, according to the frequency of their involvement in bacterial endocarditis, as (1) bicuspid aortic valves, (2) patent ductus arteriosus, and (3) interventricular septal defects. With regard to the associated findings of acute bacterial endocarditis and bicuspid aortic valve, it must be remembered that a number of reported so-called congenital bicuspid aortic valves are not "congenital" but are acquired, i.e., of inflammatory origin (Koletsky, 1943).

Gelfman and Levine (1942) found, among 31,023 autopsies, 453 instances of congenital heart disease involving persons of all ages, 181 of whom were over two years old. Bacterial endocarditis was superimposed on the congenital defect 35 times (06 per cent) in the whole group and 30 times (16.6 per cent) in the group of patients who were over two years of age. Twenty-five of the 181 hearts with congenital defects were further complicated by rheumatic infection. Table X-13 is taken from Gelfman and

and Levine's article, to show the type of congenital anomaly involved by endocarditis.

Among Abbott's (1927-28) 200 recorded cases of *coarctation of the aorta*, there were 14 with mycotic arteritis and mycotic aneurysms. In Gelfman and Levine's series, no instance of acute endocarditis was found on interatrial septal defects. Abbott stated, in a communication to O. A. Abbott (1941), that she had encountered, among 850 congenital intracardiac defects, only one instance of subacute bacterial endocarditis superimposed on a lower atrial defect. Saphir (1933) found a recent verrucous (rheumatic) endocarditis at the margin of the foramen ovale on its right atrial surface. There was also present an acute verrucous endocarditis superimposed on an old endocarditis of the mitral valve. Geiger and Anderson (1947) reported an instance of an interatrial septal defect and mitral stenosis, complicated by bacterial endocarditis. They also referred to 2 other cases in the literature. Sussman and Price (1952) encountered subacute bacterial endocarditis about a patent foramen ovale in an otherwise normal heart. It may be of interest to mention here an instance of a postoperative acute bacterial endocarditis (gram-positive diplococci) superimposed on a congenital interatrial septal defect in a dog (O. A. Abbott, 1941).

More and more instances are appearing in the literature of cures of acute and subacute bacterial endocarditis (endarteritis) in which the bacterial lesion was superimposed on a patent ductus arteriosus. Cure is accomplished by surgical ligation of the ductus (Vesell and Kross, 1946, Ziegler, 1946). The difficulties in deciding whether to operate concern the medical skill, not only in diagnosing the condition, but also in ruling out the simultaneous presence of acute endocarditis of one of the valves. A number of instances are on record in which the acute endocarditis or endarteritis had involved, not only the region of the congenital anomaly, but also one or more valves (Furlong, 1944, Antenucci and Eckhardt, 1942).

Bacterial Endocarditis Superimposed on Syphilitic Aortic Valve. Libman in 1917 discussed the infrequency with which subacute bacterial endocarditis attacks valves previously damaged by syphilis. Rosenberg (1940, consult for literature) in a critical

analysis, stated that up to 1940 there were reported only 10 proved instances of bacterial endocarditis superimposed on syphilitic aortic valvular disease.

Wright and Zeek (1940) reported 5 cases of bacterial endocarditis superimposed on syphilitic valvular disease. They definitely ruled out a congenital anomaly or rheumatic type of valvulitis as the primary disease. They also stated that they had encountered 7 additional instances of acute bacterial endocarditis associated with syphilitic aortitis but without syphilitic involvement of the aortic valve. It is of interest to mention here Forster's (1939) report of an instance of *Salmonella suispestifer* endocarditis superimposed upon a gumma of the myocardial wall. There was also a syphilitic aortitis, but the endocarditis had not involved the aortic valve. Koletsky's (1942) observation of rheumatic stigmata in 4 hearts with combined syphilitic heart disease and acute bacterial endocarditis has been mentioned previously.

NONBACTERIAL (INDETERMINATE) ENDOCARDITIS

Gross and Friedberg (1936) separated forms of endocarditis which they regarded as of nonbacterial origin. At least up to the present time, neither a bacterium nor any other infectious agent has been demonstrated to cause "nonbacterial thrombotic endocarditis" and "atypical verrucous endocarditis," the so-called Libman-Sacks endocarditis.

Nonbacterial Thrombotic Endocarditis

Associated Condition. Nonbacterial thrombotic endocarditis has been known under the terms marantic endocarditis, terminal endocarditis, endocarditis simplex, and endocarditis minima. Gross and Friedberg (1936) emphasized that the various types of nonbacterial thrombotic endocarditis cannot be distinguished by the histologic appearance of the lesion. For this reason they classified 47 cases of nonbacterial thrombotic endocarditis according to the association of the latter with some significant clinical or clinicopathologic condition. Thirty-two of their 47 patients had cachectic and infectious diseases associated with chronically deformed valves, usually of rheumatic origin. Allen and Sirota (1944) reviewed the morphogenesis and significance

of nonbacterial thrombotic endocarditis and termed this condition "degenerative verrucal endocardiosis." They studied material in 50 such instances. The cause of death and the age at death in these 50 cases are given in Table X-14.



Figure X-30. Nonbacterial thrombotic endocarditis. Note presence of fibrin with few polymorphonuclear leukocytes and lymphocytes. Hematoxylin and eosin. X 250.

TABLE X-14

Cause of Death and Age at Death in 50 Unselected Cases of Active "Terminal Endocarditis" (Allen and Sirota, 1944)

A. Cause of Death	Number of Cases
Malignant neoplasm	14
Congestive heart failure	10
Major operation	7
Pneumonia	4
Acute or subacute glomerulonephritis	2
Pulmonary embolus	2
Acute suppurative pyelonephritis	2
Congenital polyposis of gastrointestinal tract	2
Ulcerative colitis	2
Blood dyscrasia	2
Coronary occlusion	1
Periarteritis nodosa	1
Congenital heart disease	1
B. Age at Death	
1-10	1
11-20	7
21-30	2
31-40	5
41-50	8
51-60	11
Above 60 years	16

Gross Features. The most striking and characteristic macroscopic feature is the presence of vegetations which are frequently somewhat larger than those associated with rheumatic endocarditis. The vegetations do not involve the mural endocardium or the pockets of the valves as do those in atypical verrucous endocarditis. The most common type of verrucous lesion is the so-called *pyramidal ridge*. This lesion consists of narrow discontinuous bands of yellow confluent deposits, superimposed on and firmly attached to a ridge-like thickening at the line of closure of a generally thickened valve. Frequently, irregular clusters of discrete or confluent, pinhead-sized yellow verrucae are superimposed on the ridge-like thickening, giving a coronal effect. Also, slightly larger, conglomerate lesions, pea-sized or even larger, are found. The tendency to involve the commissures of the mitral valve or of the aortic or pulmonic valves and, only rarely, the noduli arantii of the aortic valve, is emphasized. Usually the mitral valve is involved.

In Gross and Friedberg's series, the mitral valve was involved in all cases but one; the

aortic valve, 11 times; the tricuspid, 5 times; and the pulmonic, twice. In Moore's (1946) series, the aortic valve was the seat of the lesion 23 times; the mitral valve, 98; the pulmonic, 4; and the tricuspid, 11 times. Often, previous valvular deformities were present which were usually interpreted as old rheumatic endocarditis.

Microscopic Features. Microscopically, the vegetations consist of agglutinated blood platelet thrombi (Figure X-30), often with early evidence of organization. Along the edges of the vegetation, a lining endothelium is usually recognized. Gross and Friedberg (1936) stressed, as the most remarkable feature, the paucity or absence of inflammatory cells. Only at the base of the verrucae is there usually a slight cellular proliferation with rare capillaries. Polymorphonuclear leukocytes are not present and rarely are lymphocytes or plasma cells encountered. Neither the atrial nor the ventricular endocardium is involved. Allen and Sirota (1944) believed that the valvular lesions are characteristically hillocks of degenerated, swollen valvular collagen, occasionally with an admixture of varied amounts of serum, fibrin, platelets and red blood cells, seemingly derived from permeable or eroded blood vessels of the valves.

Interpretation. It is interesting that Allen and Sirota did not regard these lesions as thrombi, but believed them to be primarily degenerative and not inflammatory in nature, and hence, avoided use of the affix "itis." Also, they did not believe that these lesions are necessarily terminal. In fact, they stated that excrescences of Lambl (see under Tumors) are examples of such healed lesions. They also suggested that these lesions appear to be an attractive medium for ensnaring and propagating bacteria present in the general circulation, and thus constitute an important morphologic basis for the development of bacterial endocarditis. Nonbacterial thrombotic endocarditis is often reported as an incidental postmortem finding in many diseases and is obviously without appreciable clinical significance. While it does seem improbable that the verrucae themselves are of rheumatic origin, this possibility should be borne in mind. It is also possible that in some of these

instances the endocarditis might have been caused by some toxic agent. Friedberg and Gross (1936) particularly emphasized the occurrence of nonbacterial thrombotic endocarditis associated with acute thrombocytopenic purpura.

The outstanding clinical findings in these patients were fever, purpura, epistaxis, bleeding of the gums, severe anemia, low blood platelet count, retarded clot retraction, a prolonged bleeding time and a rapid downward course. In each instance the disease was clinically thought to be a general infection, even though blood cultures were sterile. At autopsy the spleen was enlarged in all 3 of their reported cases. In 2 cases, there was organizing pericarditis and in the third case, there were widespread vascular lesions. Singer and associates (1947), who reviewed 12 instances of thrombotic thrombocytopenic purpura, found endocarditis associated with this condition twice.

Atypical Verrucous Endocarditis (Libman-Sacks)

Libman and Sacks in 1924 described a valvular and mural endocarditis which they termed *atypical verrucous endocarditis*. There were peculiar valvular and mural lesions which differed in morphology and localization from those encountered in acute or subacute bacterial endocarditis and rheumatic endocarditis. These vegetations were free from demonstrable microorganisms and attempts to grow bacteria from the blood proved unsuccessful. Because of the unusual character of the endocardial lesion and the presence of the verrucae, the cases were designated "atypical verrucous endocarditis." Among their 4 cases the tricuspid and mitral valves were involved 4 times, the pulmonary and aortic each twice. The mural endocardium of the right atrium was involved twice, that of the right ventricle once, of the left atrium once, and of the left ventricle four times. The vegetations on the mitral valve were situated for the most part on the line of closure but extended generally below and above the latter and also involved the free margins. The individual verrucae measured

from 1 to 4 mm. in diameter and had, in places, a rather broad attachment to the valve. In each case the inflammatory process had spread from the ventricular aspect of the posterior leaflet of the mitral valve and the line of attachment of the latter, downward along the mural endocardium of the posterior wall of the left ventricle. The lesions on the tricuspid valve were smaller than those affecting the mitral valve. Isolated areas of mural endocarditis were found quite commonly. Microscopically, the vegetations were capped by blood platelet thrombi, showing various degrees of hyaline changes, and in places the vegetations were covered by endothelium. Within the deeper layers, there were focal or diffuse cellular infiltrations, chiefly of round cells in three hearts, and predominantly of polymorphonuclear leukocytes in the remaining heart. Scattered among the inflammatory foci were numerous small hemorrhages. The valves in several instances showed diffuse fibrous thickening, similar to that resulting from previous attacks of endocarditis. In the myocardium there were neither Aschoff bodies nor any lesions similar to those encountered in either acute or subacute bacterial endocarditis.

Gross (1940) reported the results of a study of 27 hearts showing nonrheumatic verrucous endocarditis, 23 of which were from patients with disseminated acute lupus erythematosus. The valves of all of these hearts were studied regardless of whether they showed gross endocardial lesions. On microscopic examination he found lesions in all of the 23 hearts. These were present particularly in the valve rings, valve leaflets, valve pockets, mural endocardium and pericardium. Among these 23 hearts, lesions were observed in the mitral ring 11 times; in the tricuspid, 12; in the pulmonary, 8; and in the aortic ring, 4 times. The gross and microscopic appearances of the lesions were similar to those described by Libman and Sacks. Gross emphasized that the verrucae occurred frequently, were generally widespread, and were often present in the pockets of attachment of the chordae tendineae to the valve, along the chordae themselves, and on the chordal attachments to the papillary muscle ("pocket lesion"). No gross ulcerations or perforations of the valves were found. Microscopically, the earliest lesions

ed of cellular proliferations and degenerations on the surface of the valve. The rating cells sometimes appeared to be enial cells, but more often they were fibro-or large mononuclear cells.

nphreys (1948), also, stated that the endo-lesions sometimes were difficult to detect. hearts which she studied, the lesions had ie almost completely organized. She stated hey may be far from obvious, if they are nd spread on the valvular surfaces or if are hidden beneath the cusps or in the r regions between the muscular trabeculae.

ier lesions Libman and Sacks found, of their 4 cases, an organizing fibrinous rditis. They also reported the presence patients of diffuse glomerulonephritis i was acute in one and subacute in the

Baehr and associates (1935) described striking vascular lesions in the kidneys and other organs. Klemperer and associates (1941) particularly stressed the so-called "wire-loop" changes in the renal glomeruli. Libman and Sacks had already noted that 2 of their original 4 patients had an eruption of the face, which resembled acute disseminated lupus erythematosus. Klemperer and associates studied 20 cases of lupus erythematosus and, interestingly enough, found this type of endocarditis in 12 (60 per cent). In 8 (40 per cent) of these 20 cases, the lesions were recognized on gross examination and in 4, only on microscopic examination. These authors emphasized that disseminated lupus erythematosus is founded, morphologically, on a well-defined series of alterations of the collagenous tissues, and that the alterations also form the basis of the atypical verrucous endocarditis.

EXPERIMENTAL BACTERIAL ENDOCARDITIS

spite many studies of experimental pro-on of bacterial endocarditis, principally e rabbit and dog, Hadfield and Garrod 7) have remarked that little has been d to our knowledge of the disease.

e earlier literature is reviewed by Ribbert 4). In the older experiments, the various s in the experimental animals were injured a probe, and streptococci or staphylococci injected intravenously. Orth (1886) thought injury of the valves was the predisposing nt. Later, Ribbert produced bacterial enditis by the intravenous injection of staphy-ci mixed with finely ground particles of o. Horder (1908-09) produced endocarditis bbits by intravenous injection of streptococci ned from a patient with subacute bacterial carditis. Rosenow (1912) reported experi-al endocarditis following injection of bac-that caused the disease. He attributed the carditis to embolism of the vessels of the s. In regard to so-called elective localization reptococci, as postulated by some investiga-Karsner (1955) stated that there is no coning evidence that organisms have a special ity for the endocardium. MacNeal and asso-s (1939) produced endocarditis in 27 of 57 its by repeated large intravenous doses of tococci derived from patients with bacterial xarditis. Later MacNeal and associates

(1943, 1944, 1945) in similar experiments, found cocci early, widely distributed in the superficial cells of the endocardium. Large vegetations, most often on the mitral valve, were found in rabbits surviving more than a few days.

It is interesting that Kinsella and Muether (1938) were unable to produce endocarditis in dogs by injecting streptococci. Only after the valves had been injured mechanically were they able to produce endocarditis by intravenous or oral administration of the organisms. Friedman and co-workers (1938) reported the production of infected vegetations on the leaflets of the cardiac valves in dogs, after the insertion into the cardiac cavity of a small, hollow bakelite capsule filled with blood agar culture of *Str. viridans*. They encountered the vegetations in 4 of 13 dogs. Loewe and associates (1946) also attempted to show that only a particular type of *Str. viridans* produces bacterial endocarditis (q.s.).

Much attention has been focused on the preparatory injection of a substance thought to predispose the experimental animal to the development of endocarditis. The preliminary injection of vaccine, casein, or other substance usually administered subcutaneously or intravenously, is followed, after a varying period of time, by an intravenous injection of virulent bacteria (Thomson, 1935; Dietrich,

1937). (See also Pathogenesis of Rheumatic Disease, page 649.)

Because of these experiments the research of Bland and associates (1939) is particularly noteworthy. Following one or more injections of streptococci, isolated from the lung of a dog that died from pneumonia, these investigators observed bacterial endocarditis in 40 per cent of 25 dogs which had not received any preparatory treatment, and in which the heart valves were not previously injured. In fact, in 4 dogs endocarditis developed after a single intravenous injection. It was suggested that the use of a virulent strain, isolated from the same species, contributed to the positive results. From the literature in

general, it would seem that several factors are involved in the development of endocarditis. However, the experiments of Bland and associates indicate that the presence of multiple factors is not essential, since virulent organisms alone may cause acute bacterial endocarditis in a previously healthy animal. Dick and Schwartz (1946) confirmed that bacterial endocarditis may be produced in dogs by a single injection of organisms without previous injury to the cardiac valves. Although it is clear from these references that acute bacterial endocarditis can be produced in various ways in the experimental animal, typical subacute bacterial endocarditis has not been produced.

SYPHILITIC LESIONS

Syphilis of Aortic Valve

If syphilitic aortitis occurs at the root of the aorta it may cause narrowing or closure of the mouth of one or both of the coronary arteries and, because of the involvement of the aortic valve or aortic ring area, insufficiency of this valve. (See Syphilitic Aortitis, page 906.)

Heller (1899) and Chiari (1904), in their classic descriptions of syphilitic aortitis, stated that the syphilitic process of the aorta may involve the aortic valve, causing insufficiency of this valve. However, it was not until 1920 that Lupu reported the results of a rather extensive microscopic study of the valve area.

Gross Lesions. Few lesions are as characteristic grossly as syphilitic involvement of the aortic valve (Figure X-31). Normally, the free edges of adjacent aortic cusps are attached at points on the intima of the aorta, called commissures. In syphilis, the commissures are widened. This separation of the cusps at the commissures may involve an area 1 or 2 mm. or more in width. Commonly hyaline plaques, often triangular in shape, are present in the regions of the commissures. Such a separation or widening of the commissures is pathognomonic of syphi-

lis. It is obvious that the widening of the commissures must interfere with the proper closure of the valve during diastole, and that such a valve must be insufficient. The location of the leak is within the region of the widened commissure. Often, too, the more

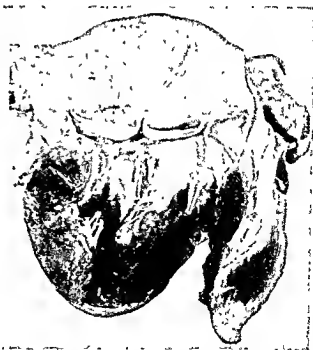


Figure X-31. Syphilitic aortitis and aortic insufficiency. Note narrowing of ostium of right coronary artery, syphilitic aortic valvulitis and separation of cusps at commissures. (WCGH, 45 A 268.)



Figure X-32. Extreme widening of the commissures. A pointer is directed to the sinus of Valsalva corresponding to the posterior aortic cusp which is almost completely obliterated. Note marked separation the cusps at commissure between the posterior and the anterior cusps. The interventricular septum presents several diastolic endocardial pockets.

centrally located portions of the free margins of the cusps show thickenings, eversion, rolling or curling, and sometimes retraction. The adjacent aorta almost invariably is the seat of the characteristic syphilitic lesions, with varying numbers of red, depressed scars, sinuses or grooves, combined with varying degrees of intimal fibrosis, foci of hyalinization and calcification. Often, too, the root of the aorta or certain regions of the ascending aorta show aneurysmal dilatations. The mouth of one or both coronary arteries is often narrowed. Sometimes the syphilitic process is observed only in the proximal segment of the ascending aorta.

Microscopic Changes. Saphir and Scott (1927) studied an apparently very early case of syphilitic aortitis, with involvement of the aortic valve. In this early instance, only widening and no hyalinization of the commissures was encountered. From a histologic study of this case and of 70 more advanced cases, they concluded that very early lesions occur between the intima of the

sinus of Valsalva and the corresponding lateral and proximal portions of the aortic cusps, and that these adhesions cause separation of the commissures. Histologically, the intima of the structures of the sinus of Valsalva and the corresponding lateral portions of the cusps first showed degenerative and later, inflammatory changes. Coincident with the inflammation, a number of blood vessels extended from the adventitia through the intima to the involved commissures and lateral portions of the cusps. Newly formed vessels also extended from the base of the cusps to their lateral and proximal borders. Fibroblasts, endothelial leukocytes and lymphocytes were the predominating types of cells. In later instances, hyalinization of the intima in the region of the commissures was often encountered. Histologic examination of the more central portions of the cusps, which grossly disclosed thickening and rolling, showed only fibrosis and hyalinization, with very few cellular elements and no newly formed blood vessels. Saphir and Scott believed that these areas of thickening in the center of the cusps were caused by the continuous mechanical pressure of the regurgitating blood, after the insufficiency of the valve had been established. The centrally located margins of the cusps in early cases were neither thickened nor rolled.

Pathogenesis. If it is true that widening of the commissures is primarily the result of adhesions between the lateral portions of the aortic cusps and the adjacent aortic intima of the sinus of Valsalva, one would expect that the process sometimes would advance to the more central portions of the cusp and corresponding intima of the aortic wall of the sinus of Valsalva; that the adhesions would not necessarily be confined to the commissures but might extend toward the center of one or both adjacent cusps, with consequent adhesions between the cusps and the aortic intima of the corresponding sinus of Valsalva over a wide area. Such adhesions would lead to severe narrowing of the respective sinus of Valsalva, or perhaps even to obliteration of the sinus, or the transformation of the

sinus into a blood-filled cavity with resulting extreme regurgitation of the valve.

Interestingly enough, 2 such instances have been encountered by Saphir and Stasney (1933). In 1 of these (Figure X-32), one sinus of Valsalva was actually transformed into a blind cavity and in the other, a part of the sinus had almost completely disappeared because of widespread adhesions between the aortic intima and large portions of the cusp. These authors found only 8 similar cases in the literature. Particularly pertinent is one described by Roktansky and reported by Maresch (1931). It was labelled, as translated from Latin by Maresch, as follows. "A dilated and hypertrophic heart with the large vessels from a 50-year-old woman. At the root of the dilated and thickened aorta, the right valve, because of adhesions to the vessel, appears absent and the mouth of the coronary artery obliterated." Jason (1941), who also studied syphilitic deformity of the aortic valve in 27 hearts, did not emphasize differences of the central and lateral portions of the cusps. He concluded that all of the valve distortions appeared to have been caused by two processes: (a) a destructive inflammation of the aortic wall resulting in destruction and dislodgement of the attachments of the cusps at the commissures, and (b) a reparative fibrosis. However, it would seem difficult to explain the extreme involvement of the aortic valve in syphilis, as related above, on this basis. Just why there is a predilection of syphilis for the base of the aorta and the region of the commissure is difficult to explain. Saphir and Scott (1927) believed that this area of the aorta shows more vasa vasorum than any other region of the aorta. This is in agreement with Spalteholz. Syphilis is a primary disease of the vasa vasorum and, therefore, has greater significance in areas containing a large number of vasa vasorum. It appears in the vast majority of cases that syphilitic valve lesions occur only with involvement of this segment of the aorta. *Spirochetes* have been demonstrated in the aortic valve involved by syphilis. Sisk and Raska (1935) reported the lesion in 2 adults, in 1 of whom numerous spirochetes could be demonstrated by Kanzler's method. Only a few spirochetes were found in the heart of the second patient.

Gumma of Aortic Valve. Invasion of the heart valves by gummata is also described in the literature. Richter (1936) found in the literature only 8 adequately described in-

stances of *gummatous endocarditis* of the *aortic valve*, resulting from invasion of the cusps by a syphilitic process in the root of the aorta or from a gumma of the interventricular septum. He described an instance of gummatous endocarditis of the aortic valve in which the *Treponema pallidum* was demonstrated. In this instance, a congenital bicuspid aortic valve and subaortic stenosis also were present.

Cases are on record of combined syphilitic and rheumatic aortic valvulitis (Figure X-28). Lisa and associates (1942) reported 9 such instances.

There are also many instances of syphilitic aortitis without separation of the commissures but with severe dilatation or "stretching" of the root of the aorta, including the sinus of Valsalva, with resulting insufficiency of the aortic valve. This stretching of the aortic ring is the result of the syphilitic process in the adventitia and media of the aorta itself.

Patients with syphilitic aortic insufficiency and stenosis of the mouth of one coronary artery often succumb unexpectedly. Martland (1930) found at autopsy that, in 101 cases of sudden death caused by syphilis of the aorta and heart, aortic regurgitation was the predominating lesion in 36 cases, and stenosis and atresia of the coronary ostia in 15.

Syphilitic Coronary Arteritis

Histologic Changes at Mouth of Coronary Artery. Such changes have been studied by Burch and Winsor (1942). The adventitia of the coronary arteries showed an accumulation of small round cells, particularly about the vasa vasorum. The inflammation usually begins (Moritz, 1931) about the vasa vasorum in the adventitia of the vessels and extends along the smaller vessels into the media and intima. The media becomes infiltrated with lymphocytes and small round cells, which replace the healthy muscle and elastic tissue. The intima is greatly thickened, as a result of the formation of succulent vascular inflammatory plaques which occlude the ostia of the coronary arteries in the regions where they pass through the aortic wall. Such exu-

edematous lesions may encircle the aortic root, forming the so-called "girdle of Venus" (Leary, 1940). When the coronary ostia are involved, usually only the first 3 mm. of the artery are affected, and beyond this point the vessel is wider and remains patent throughout its entire length.

Syphilis of Mitral Valve. Syphilis of the mitral valve has been a much disputed subject in the older literature. The fact that syphilitic aortic insufficiency may be present in a patient who also happened to have an old inflammatory lesion of the mitral valve with or without functional disturbances, does not at all imply that the mitral lesion is also syphilitic.

On the contrary, it is probable that such a mitral lesion is invariably coincidental, the result of a nonspecific inflammation or of a rheumatic infection.

Blackman (1935) stated that extensive syphilitic lesions of the mitral valve have rarely been described. In the 2 hearts reported by Blackman, syphilitic changes were continuous with syphilitic lesions at the root of the aorta and the aortic valves, and were present in the membranous septum of the heart and the aortic leaf of the mitral valve. Grossly, the lesions consisted of a diffuse leathery thickening of these areas. Microscopi-

cally, gummatous necrosis or dense vascular scars with perivascular round cell infiltrations were found. It is interesting that only the aortic leaflet of the mitral valve was involved. It must be emphasized that there are only two extremely rare possibilities for involvement of the mitral valve in syphilis. Either a gumma may be present in the mitral valve or the adjacent myocardium, with secondary extension into a leaflet, or the syphilitic process may extend from the base of the aortic valve downward to the aortic leaflet of the mitral valve.

Such instances, however, are so rare that it may be stated that syphilis practically never involves the mitral valve.

Syphilis of Pulmonary and Tricuspid Valves. Syphilis may, extremely rarely, involve the pulmonary valve; such instances are always associated with syphilitic pulmonary arteritis.

Plenge's (1929) second case showed involvement of the pulmonary valve. Another clear-cut instance was reported by De Navasquez (1942). There was a syphilitic pulmonary arteritis and the pulmonary valves disclosed typical widening of the commissures. Gummatous involvement of the pulmonary and tricuspid valves, in addition to the mitral valve, have also been reported (Richter, 1936).

CONGENITAL (FETAL) VALVULAR ENDOCARDITIS

In the older literature there are a number of reports of so-called fetal endocarditis (Figure X-33).

Ribbert (1924) maintained that such an endocarditis could occur during the last month of gestation and only after the valves had been well formed. He thought that the occurrence of such a fetal endocarditis was rare. Though fetal endocarditis, as characterized by the presence of a verrucous vegetative inflammation, has never been observed, he asserted that it might be recognized in an end-stage by the presence of fibrous thickening in the valves. He emphasized great difficulties in interpreting older valvular lesions in infants, and that often one cannot decide whether they are the result of an old endocarditis or of a congenital malformation. Ribbert pointed to the relatively frequent combination of so-called endocarditis and malformation of the heart. He stated that, either during the fetal period or

shortly after delivery, the inflammatory processes were probably superimposed upon a congenitally malformed valve. Cappelli (1933) noted microscopic changes in many fetal hearts, which he interpreted as valvular endocarditis. However, P. Gross (1941) thought that the significance of these observations appears rather dubious in view of the frequency (76 per cent of 67 unselected cases) with which these lesions were found. Gross stated that a careful analysis of the cases reported in the literature reveals that myocardial scars or myocardial fibrosis, prerequisites for the diagnosis of fetal endocarditis, was noted in 78 per cent of the cases listed as fetal endocarditis. On the other hand, these lesions have been thought to represent non-inflammatory changes. A number of writers noted that the papillary muscles showed the most marked lesions in "fetal cardiac inflammations." These observations may be matched by reports of similar alterations which are regarded as non-inflammatory. Valvular ex-

creescences, often termed vegetations, were noted in 11 of 53 cases designated as fetal endocarditis, and in 4 of 23 cases in which this diagnosis was made in the material collected by Gross.

In the few instances in which the valves were examined histologically, the excrescences were described as composed of embryonic connective tissue. In not a single instance was there unequivocal evidence of inflammation. Thus, Gross concluded that the occurrence of fetal endocarditis has never been established. The macroscopic and microscopic abnormalities which have been regarded as criteria for the diagnosis of fetal endocarditis, have been observed also in the presence of congenital cardiac defects and, after study, have been interpreted as non-inflammatory lesions. The valvular changes seen in these cases are better explained on the basis of a developmental defect, since they show no inflammatory residua. From examination of a large number of hearts with various congenital anomalies, and deformities of valves, we must also agree with Gross' findings. The red gelatinous material, simulating broad-based, smooth vegetations which is occasionally encountered in infants' hearts (Figure X-33), constitutes the remains of a myxomatous mesenchymal tissue and cannot be regarded as organizing vegetations. True residua of inflammation are never present.

McDonald (1950) described valvular thrombotic vegetations in a newborn. These were interpreted as bland thrombi which had formed on surface irregularities in the development of valvular hematomas, or as a result of hypothetical rupture of blood cysts found on the cardiac valves of the newborn. The possibility was also suggested that this lesion may be identical with the exudative type of verruca found in degenerative verrucal endocardiosis described by Allen and Sirota (see page 751).

Bohmig and Klein (1953) examined the heart

valves of 29 stillborn and newborn infants, and found glossy nodules in 5. Microscopically, they described a serous type of inflammation. They believed that serous endocarditis is common among malformations of the heart valves, but remarked that these changes in the valvular apparatus occur in the absence of bacteria.

White-pink, apparently edematous, nodules in the region of the attachment of the chordae tendineae to the atrioventricular valves are occasionally found in children and are referred to as *noduli albini*. They consist of myxomatous material and may be regarded as remnants of portions of the original endocardial cushion. They are of no clinical significance.



Figure X-33. So-called congenital endocarditis of pulmonary valve. This is not a true endocarditis, but the valves still show material constituting the original endocardial cushion.

PARIETAL ENDOCARDIAL FIBROSIS (SCLEROSIS)

Congenital Endocardial Fibroclastosis

Gross (1941) devoted considerable attention to opaque, glistening, white or yellow-white thickenings of the parietal endocardium

(Figure X-34) in infants' hearts, with or without valvular deformity. These lesions had been classified as fetal inflammation by some investigators, and as developmental anom-

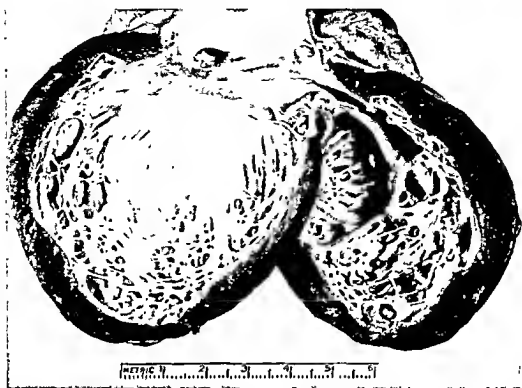


Figure X-34. Congenital fibroelastosis of left ventricle in 18-month-old boy. Heart weighed 135 Gm, compared to normal average weight of 52 Gm. (Courtesy of Dr. Walter A. Stryker.) (WCGH, 58 P 96.)

alies by others. He emphasized that diffuse endocardial fibrosis is devoid of inflammatory residua and is best explained as simple hyperplasia of the endocardial fibroelastic tissue. The decision as to whether this is secondary to circulatory changes or is a primary developmental defect is easier to make in those cases in which such endocardial sclerosis is found unassociated with valvular defects. Such cases are to be found in the literature (see Gross). Thus, Gross classified these parietal endocardial changes, not as an inflammatory lesion, but as a developmental defect. Sano and Anderson (1942), in discussing endocardial fibrosis in infants, spoke of "endocardial hyperplasia" which they encountered in 3 instances. They were impressed with the large amount of elastic or fibroelastic tissue within the white endocardium, as demonstrated by special stains.

Weinberg and Himelfarb (1943) reported on two infant siblings, the heart of one having a diffuse gray-white thickened endocardium confined to the left ventricle, while the heart of the other had additional tiny foci of endocardial thickenings in the right atrium and ventricle. The

first infant also had a severely narrowed ascending aorta proximal to the obliterated ductus arteriosus.

Microscopically, the thickening of the endocardium was produced mainly by an increase of elastic fibers and partly by collagenous fibers. They applied the term *fibroelastosis* (Figure X-35) to this lesion. The occurrence of fibroelastosis in siblings and the absence of a history of any infection in the mother during the period of pregnancy militate against the concept of fetal endocarditis as an intra-uterine infection, and support the suspicion of an inherent developmental defect.

The most generally accepted term for this condition is fibroelastosis. Thomas and associates (1951) found among 10,000 autopsies, 24 cases of chronic heart disease with hypertrophy of uncertain cause. Twenty of these showed abnormal degrees of fibroelastosis. They remarked that in some instances of so-called congenital hypertrophy of the heart, the underlying disease probably was fibroelastosis.

Weinberg and Himelfarb thought that the



Figure X-35 Congenital fibroelastosis of left ventricle, from heart shown in Figure X-34. Verhoeff-van Gieson X 100. (WCGH, 58 P 145.)

endocardial fibroelastosis can explain the failure of the heart. They felt that with the development of such a thick fibroelastic layer, one could postulate some interference with emptying of the arterioluminal vessels into the ventricle, because of constriction of their orifices by the elastic tissue. Thus, with the establishment of obstruction to the flow of blood, partial stasis may develop within the intramyocardial capillaries. This leads to some degree of anoxemia and eventually to myocardial damage and myocardial failure.

Cosgrove and Kaump (1946) studied endocardial sclerosis in infants and children. Almost all of their patients showed evidence of congenital anomalies. They particularly stressed that the microscopic appearance of the valve rings, with the myxomatous stroma and absence of lymphocytes and polymorphonuclear leukocytes, calls to mind congenital rests. Although myocardial lesions were present, they resembled infarctions rather than inflammatory lesions. This appearance, together with the relatively complete occlusion of the smaller arterial and venous channels, emphasizes the probability of the congenital nature of primary endocardial sclerosis.

Craig (1949) described congenital endocardial sclerosis in 37 instances of congenital heart disease. In the majority of these cases, there was an asso-

ciated malformation of the valves. It was noted that this lesion occurred more commonly in males than in females and was found much more often in the left ventricle than in the right ventricle. He discussed the various theories of causation of endocardial sclerosis and refuted all of them. It seemed most likely to him that both the valve lesions and the endocardial lesions were the result of abnormalities of development rather than of an infectious process. Myocardial degeneration and fibrosis were frequently present in the subendocardium. This was thought to be the result of anoxemia.

Prior and Wyatt (1950) expressed the opinion that endocardial fibroelastosis may constitute a developmental disorder of mesenchymal tissue and hence may be classified with congenital cardiac malformations. They suggested the term "endocardial dysplasia" to replace "fetal endocarditis" and "endocardial fibroelastosis," both of which have misleading connotations. Johnson (1952) found fibroelastosis in hearts which showed various congenital anomalies and suggested anoxia as a cause. Stresemann (1955) reported the condition in 4 infants, and believed that a congenital metabolic disorder was the underlying cause. Thomas and associates (1954) concluded that endocardial fibroelastosis of infancy and childhood occurs on a congenital basis. They stated that the disease rarely occurs in the adult and that it is then also probably congenital, despite the lack of specificity of fibroelastosis and despite the time interval between birth and onset of symptoms. This may be true, inasmuch as the lesions in infants and in adults disclose no morphologic differences.

In this connection, it may also be mentioned that in certain instances of congenital anomalies of the heart, particularly in those which cause deviation in the direction of the normal flow of blood, there is often a diffuse thickening of the endocardium (Taussig and Semans, 1940).

In summary, the white endocardial plaques in fibroelastosis of infants consist of both connective tissue and elastic lamellae, probably are the result of developmental anomalies, and are not caused by inflammation. Clinically, the heart is large, murmurs are absent or nonspecific in nature, and cyanosis is usually absent; the appearance of myocardial failure with cyanosis is late.

Fibroelastosis in Adolescents: Evidence



Figure X-36. Endocardial fibrosis of right atrium and tricuspid valve, associated with syndrome of malignant carcinoid tumor. The leaflets of the valve are shortened and thickened and the chordae tendineae are shortened and fused (WCGH, 57 P 321.)

that some patients with endocardial fibroelastosis may survive beyond infancy was presented by Auld and Watson (1957) who reported several instances from the literature and observed fibroelastosis in a 15-year-old boy. He had been well until about 2 years before death when he developed congestive heart failure.

Fibroelastosis in Adults. Fibroelastosis has also been encountered in adults. Guraieb and Rigdon (1956) found only 24 cases in adults reported from America and England. He attributed the fibroelastosis in his patient, a 38-year-old white man, to a congenital malformation.

The interesting condition, endocardial fibrosis (fibroelastosis, endomyocardial fibrosis, and endomyocardial necrosis) of adults in various parts of Africa, is little understood. Autopsies in Uganda (Williams *et al.*, 1954), performed on certain patients

who died in heart failure, showed only *endomyocardial fibrosis*. Sometimes the fibrosis was so extensive as to obliterate the apical portion of the heart. Davies and Ball (1955), from a study of 32 autopsied cases, concluded that endomyocardial fibrosis is one of the commonest causes of heart failure in Africans in Uganda. A similar condition was thought to be prevalent in South Africa (Becker *et al.*, 1953), but was later regarded as identical with endomyocardial necrosis encountered in East Africa. Thomas and associates (1954) believed that endomyocardial fibrosis or perhaps better, *endomyocardial necrosis*, occurring in East Africans, is different from the usual endocardial fibrosis or fibroelastosis. In endomyocardial necrosis there is principally a patchy endocardial thickening and, microscopically, destruction of the original endocardium and adjacent myocardium with replacement by vascular fibrous tissue. The

elastic fibers remain as broken, irregular masses, in contrast to the intact proliferating tissue in endocardial fibroelastosis.

Fibrinoid degeneration and necrosis in the subendocardial regions have been described. This has sometimes been so severe that the term "collagenosis" has been used. Gray (1951) thought of an unrecognized parasite as a possible cause. O'Brien (1954) studied endocardial fibrosis in the Sudan. He believes that malnutrition, undernutrition, and syphilis do not play a causative role. Eosinophilia was present in only 2 of his 7 cases. He pointed out that the disease occurs commonly in Africa among Negroes, Arabs and Europeans alike, and that the cause of the condition is still unknown.

Acquired Fibrosis

Diffuse Parietal Endocardial Fibrosis (Sclerosis). In the diffuse variety of endocardial sclerosis, on opening the left ventricle, the endocardium presents a more or less diffuse white or ivory white appearance and, when incised, discloses a thickness of one or two

millimeters. The endocardial thickening may involve also the papillary muscles. A number of causes are postulated for diffuse endocardial sclerosis, the predominating ideas considering them to be the result of (1) primary lesions of the myocardium, (2) hypertension, (3) congenital anomalous origin of the coronary arteries, (4) inflammatory conditions, and (5) endocardial fibrosis associated with carcinoids.

1. Endocardial thickening may be the result of *primary lesions of the myocardium*. In many instances of large old infarcts of the myocardium, the overlying endocardium is white and thickened. Such thickening may extend over large areas and is not necessarily confined to the region of the infarct. There are two explanations for this endocardial thickening. According to one explanation, as a result of the occurrence of infarcts, aseptic



Figure X-37A. Section from right atrium of heart shown in Figure X-36. A loose fibrocollagenous tissue appears to be superimposed upon intact endocardium, the thickness of the superimposed tissue in areas being greater than the combined thickness of the underlying myocardium and epicardium. Verhoeff-van Gieson. X 16. (WCGH, 57 P 321.)

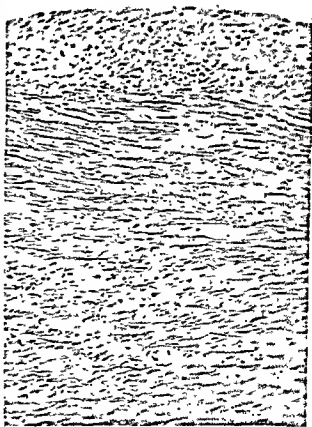


Figure X-37B. Higher magnification of subendocardial fibrous tissue shown in Figure X-37A. Note abundant pale ground-substance, thin elongated spindle cells and general resemblance to myxomatous tissue. Hematoxylin and eosin. X 160. (WCGH, 57 P 321.)

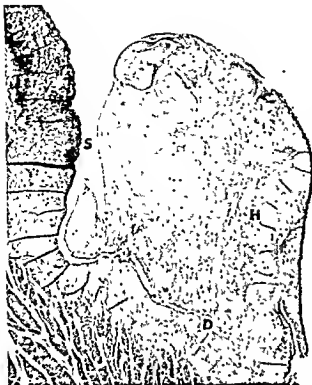


Figure X-38. Section of a cusp of pulmonary valve from heart shown in Figure X-36. The sinus (S) is almost obliterated by fibrous tissue which covers the holding surface (H) of the valve. Only scant fibrocollagenous tissue is present on the deformed surface (D) of the valve. Verhoeff-van Gieson. X 235.

mural endocarditis develops and this undergoes healing and eventually forms white scar tissue. The endocarditis corresponds to the pericarditis observed in hearts with myocardial infarcts. Such a pericarditis is not necessarily circumscribed but may be diffuse. Another explanation for such an endocardial fibrosis is that it constitutes the end stage of organized mural thrombi which had been present adjacent to the infarcted area. Such endocardial thickenings, extending over larger areas, are so significant that they should suggest the possible occurrence of old infarction. There are no elastic lamellae in these lesions.

2. A number of cases are on record of diffuse endocardial sclerosis involving particularly the endocardium of the interventricular septum. Such instances are thought to be the result of a marked permanent increase in the systolic arterial blood pressure (see Ribbert, 1924). However, such a cause has never been proved even though in functional disturbances of the various valves, circumscribed

areas of thickening are often interpreted as being the result of either systolic or regurgitating diastolic blood currents and pressure (see page 767). Yet, there are cases of endocardial fibrosis on record, particularly in children, without associated valvular abnormalities or changes in the coronary arteries or myocardial lesions. Since this endocardial sclerosis is usually found in hypertrophic hearts, hypertension has been suggested as its cause.

Taussig and Remsen (1935), in their report of essential hypertension of a 2-year-old child, referred to the endocardial lining of the left ventricle as "smooth but slightly thickened." Also, in one of Abbott's (1928) cases of coarctation of the aorta, mention was made of an endocardium that had a thick "sugar-icing."

3. Levine (1934) reported a uniformly and diffusely thickened and opaque endocardium in a 10-month-old infant. The heart was hypertrophic. There was narrowing of the descending branch of the left coronary artery and coarctation of the aorta of the infantile type. No inflammatory reaction was seen in the heart. This and other similar instances raise the question whether the endocardial fibrosis, in these cases, constitutes a congenital anomaly *per se*, as discussed above, or whether it is the result of the hypertension consequent to coarctation of the aorta. Endocardial thickening, usually associated with cardiac hypertrophy is almost invariably present in cases in which the *left coronary artery arises from the pulmonary artery*. References to the pertinent literature up to 1932 may be found in the communication by Bland and associates (1933).

Similar cases have been observed by Thomas and associates (1956); they suggested the possibility that some unknown agent caused the endocardial fibroelastosis and the calcific arterial disease which was also present in their cases. Soloff (1942) encountered many dilated blood vessels in the heart and interpreted these as a persistence of embryonic sinusoids, brought about by the lack of sufficient anastomosis between the right and the left coronary arteries. Bland and associates stated that the lack of adequate vascular supply to the myocardium seemed so severe

as to have caused not only myocardial fibrosis, but actually aneurysms of the heart. Subsequent case reports by Soloff (1942), Proescher and Baumann (1944) and Eidlow and Mackenzie (1946) described instances with hypertrophy of the heart, fibrous replacement of the myocardium and severe thickening of the endocardium of the left ventricle.

4. *Inflammation* was thought to be the underlying cause of diffuse endocardial fibrosis as reported by Comeau (1937). Both of his cases had evidence of severe myocardial damage. In one particularly, there was diffuse and focal lymphocytic infiltration with giant cells and granuloma-like lesions. He emphasized that in a group of cases of diffuse parietal endocardial sclerosis, a compensatory protective change in the endocardium is secondary to an organic subendocardial "weakness." Such a mural endocarditis obviously is the result of an extension of a primary myocarditis to the adjacent mural (parietal) endocardium. The endocardial sclerosis is the final result of the mural endocarditis in these instances.

Löffler (1947) described "endocarditis parietalis fibroplastica," in which the parietal endocardium of both ventricles is thickened but the valves are normal. This entity is often accompanied by eosinophilia, particularly in its early stages. Because occasionally streptococci were cultured from the various organs (so-called dissociated streptococci), and because in one case Lohlein's nephritis was encountered, Löffler believed this disease to be somehow related to subacute bacterial endocarditis. Egger (1944) described a similar condition under the term "endocarditis obliterans" and linked it to endarteritis obliterans (Buerger's disease). In Egger's case the associated clinical findings were severe dyspnea, cyanosis, enlargement of the liver, edema of the lower extremities, ascites and hydrothorax. The differential leukocyte count disclosed an eosinophilia of 15 per cent. The mural endocardium of both the right and left ventricles was severely thickened and covered with thrombi. The lumen of the left ventricle was narrowed to the diameter of the lumen of the ascending aorta. The valvular apparatus was intact and the coronary arteries were unchanged. Microscopic examination disclosed subacute and chronic inflammation, with predominance of

lymphocytes and plasma cells in both the endocardium and adjacent myocardium. Perivascular inflammatory cells were frequent and granulation tissue and young connective tissue were present. Despite a history of rheumatic fever, Egger thought that the inflammatory disease of the myocardium and the mural endocardium should be classified as allergic. Lennox (1948) reviewed the literature and gave data on 6 such instances. He described, in a 53-year-old woman who had eosinophilia and died of status asthmaticus, an extensive cellular infiltration of the endocardium of the left ventricle. He thought that a secondary mural thrombosis followed by organization would exactly duplicate the end result of Löffler's endocarditis. Popp and Zandanell (1955) reported an instance and reviewed the literature. Their patient also had an old valvular endocarditis, mural thrombosis and fibrosis of the myocardium with inflammatory cells. In addition, the patient had syphilitic aortitis.

5. *Endocardial fibrosis associated with malignant carcinoid tumor.* Lembeck (1952) observed that argentaffine tumors (carcinoid) contain large amounts of serotonin (or enteramine) which is apparently responsible for a clinical picture of intermittent cyanotic flushing, fluctuations of blood pressure, diarrhea, and "asthma." At autopsy in a number of cases with intestinal argentaffine carcinoma with metastasis, endocardial fibrosis of the right side of the heart, of the pulmonic valve (Figures X-36 to 38), and of the tricuspid valve have been reported. It may be surmised that this fibrosis is most likely caused by an excess of serotonin in the blood, since the lesions are usually not seen in the left side of the heart (Waldenstrom and Ljungberg, 1955).

This is explained by the observation that the lungs remove serotonin by oxidizing it to the inactive 5-hydroxyindole acetic acid. Only when there is a right-to-left shunt may the endocardium and valves of the left side of the heart become involved, as was shown in the case with the patent foramen ovale reported by McKusick (1956). It appears that the endocardial change is caused primarily by the malignant argentaffine tumor having large metastatic growth, often in the liver.

Histologically, the pulmonary valve has fibrosis or even cartilage-like fibrous scarring, with or without gross deformity. Mono-



Figure X-39. Multiple localized areas of endocardial fibrosis. Old endocarditis of mitral and aortic valves.

nuclear cells and lymphocytes may be noted near the endocardial surface. Often the right atrium also is involved. The cordae tendineae may be considerably thickened. Coble and associates (1956) emphasized sclerotic thickening of the cusps, often with fusion of the commissures. In their case, there was almost no inflammatory reaction. They thought that the high concentration of serotonin in the blood of the right side of the heart may alter the endothelium by increasing cellular permeability and allowing deposition of platelets on the valve cusps, with subsequent fibrosis.

Up to 1955, 23 probable cases had been reported (Coble *et al.*, 1956).

Circumscribed Parietal Endocardial Fibrosis (Sclerosis). Circumscribed fibrous thickenings of the endocardium, so-called *circumscribed endocardial sclerosis*, is common (Figure X-39). It is usually present in the left ventricle and often involves the endocardium covering the interventricular septum, but is also occasionally found in the right ventricle and in the left atrium. It is sometimes difficult to decide whether such localized endo-

cardial fibrosis is the result of a preceding primary inflammation, an underlying infarct (see page 702), or abnormal blood currents and eddies in functional disturbances of the heart valves. Of particular interest are the latter. Areas of circumscribed endocardial fibrosis are often present in association with insufficiency of the aortic valve. In such cases, the thickened plaques may be found anywhere in the left ventricle with the exception of the posterior wall and of the apical portions of the heart. Most commonly they are present on the interventricular septum, and not rarely on the endocardium of the aortic leaflet of the mitral valve and bridging over the trabeculae carneae. Because such a circumscribed endocardial fibrosis so often accompanies aortic insufficiency, Zahn (1895) thought that these simple endocardial thickenings were produced by the continuous irritation of the impulses of the regurgitating blood. He also observed circumscribed endocardial sclerosis in the left atrium in instances of insufficiency of the mitral valve. However, others (Ziegler, 1908; Aschoff, 1919) empha-

sized that circumscribed endocardial fibrosis (sclerosis) is often primarily inflammatory in nature, representing the end stage of acute mural endocarditis. This view is supported by the frequent finding of circumscribed endocardial fibrosis in hearts which are the seat of old inflammatory valvular conditions. Yet, it is well known that rheumatic endocarditis, which probably is the most common cause of valvular deformities, does not cause ventricular mural endocarditis. Besides, circum-

scribed endocardial fibrosis is often seen in instances of syphilitic aortic insufficiency while syphilitic inflammation does not involve the mural endocardium. Thus, the genesis of circumscribed endocardial fibrosis, at least in these instances, cannot be primarily inflammatory. In histologic studies of such circumscribed endocardial fibrosis, rarely will one encounter inflammatory changes (Saphir, 1930). The histologic changes will be discussed below.

ENDOCARDIAL POCKETS

Endocardial pockets, imitating the shape of valve cusps, are a striking finding in some cases of insufficiency of the aortic valve. They are most commonly situated on the *interventricular septum of the left ventricle* and are referred to in the older literature as Zalin's (1895) or Schmincke's (1908) pockets. They are often multiple with their openings directed toward the aorta. More rarely, pockets are observed just *beneath the aortic valve* with their openings directed toward the apex of the heart. In such instances there is also stenosis of the orifice of the aortic valve or an actual or relative narrowing of the aortic conus. Much rarer are endocardial pockets in the *left atrium*; here the openings are usually directed toward the mitral valve which invariably is insufficient. Though endocardial pockets are not rare, they have received little attention. In the field of pathology, few anatomic structures are so characteristic as to indicate a definite functional disturbance. The relevant literature is given by Saphir (1930). These lesions arise principally as circumscribed endocardial thickenings, before they become fully established as pockets. While it is possible that some endocardial thickenings are the result of a circumscribed primary mural endocarditis, it seems much more likely that the primary endocardial fibrosis is the result of an abnormal regurgitating column of blood or perhaps pressure, with the formation of eddies. In stenosis of the aortic orifice or of the conus of the left ventricle, it is possible that the friction of the systolic blood stream and pressure produces me-

chanical irritation of an area situated at the entrance into the stenosed region. (The conus aorticus, often called conus arteriosus sinister, is the most cephalic portion of the left ventricle located just inferior to the aortic valve; Krasso, 1925.)

Diastolic Pockets. In insufficiency of the aortic valve, the continuous impact of the regurgitating diastolic column of blood exerted upon a localized area of young connective tissue may well undermine this tissue and produce a pocket with its opening directed toward the aortic valve (Figure X-40). Ing-ham and Henthorne (1938) stated that, for



Figure X-40. Circumscribed endocardial thickening and diastolic pocket characteristic of insufficiency of aortic valve.



Figure X-41. Atrial pocket facing open foramen ovale.

want of a fuller explanation of the cause of these lesions, the theory of mechanical irritation of the endocardium caused by abnormal blood currents is accepted as the most logical. Krasso (1925) named such pockets *diastolic pockets*. Diastolic pockets are found more often in hearts with syphilitic aortic insufficiency than in hearts with insufficiency of the aortic valve from other causes. Because the insufficiency of this valve resulting from syphilis is brought about by the separation of the cusps at the commissures, the path of the regurgitating blood is narrow and seemingly more rigid (Kaewel, 1928) than in the insufficiency which results from retraction of the cusps. In some instances only one or two pockets are found; in others, actually rows of 3 or 4, sometimes at different levels. This may indicate a gradual increase in the degree of insufficiency. Saphir emphasized that the presence of diastolic pockets on the interventricular septum of the left ventricle is pathognomonic of insufficiency of the aortic valve.

Systolic Pockets. Sometimes pockets are found on the interventricular septum, their openings directed towards the apex. Krasso (1929) called such pockets *systolic pockets*. It seems that the continuous pressure exerted upon the entrance of a stenosed aortic conus,

or upon the mural endocardium just below a stenosed aortic valve orifice, may undermine a localized area of early fibrosis and produce a systolic pocket. In Saphir's (1930) series, systolic pockets were encountered more often in instances of relative stenosis of the aortic conus in hypertrophied and dilated hearts. Systolic pockets are also found in the left atrium above the mitral valve, in association with insufficiency of this valve. The opening of the pockets is directed towards the mitral valve. Atrial pockets are much rarer than ventricular pockets.

Hellerstein (1947) concluded that prolonged regurgitation of blood and the resulting pressure are the most significant factors in the development of these endocardial pockets.

Microscopically, Ingham and Henthorne (1938) found the cusps of these pockets or pseudovalves to be composed of the loose form of adult connective tissue peculiar to normal heart valves. The subendocardial elastic tissue was split to form lamellae on both the inner and outer surfaces of the pseudovalve and also provided a fine elastic meshwork for the connective tissue structure. There was no evidence of inflammatory reaction at the base of this pocket. A definite hyaline thickening of the endocardium was found close to it. They emphasized that the pseudovalve or pocket had every appearance of a normal young heart valve. Hellerstein (1947) also described reduplication of the elastic fibers above and below the pockets and extension of the elastic lamellae from the endocardium into the pockets. He, too, remarked on the absence of any vestiges of inflammation. Saphir, however, in a few pockets demonstrated blood vessels and residua of inflammation.

Significance. Thus, it would seem that the presence of pockets materially aids in the diagnosis either of insufficiency of a valve or of stenosis of a valve orifice or aortic conus. The original young connective tissue formation is seldom primarily the result of a mural endocarditis, but much more often the result of mechanical irritation. Once circumscribed young connective tissue is formed, continu-

ous pressure and mechanical irritation will cause a secondary excavation and the formation of a pocket or pseudovalue. Depending upon the direction of the irritating blood column and mechanical trauma, the pocket will show an opening directed either toward the valve or away from it.

Wilke (1910) and also Borst (1919) stated that such pockets are manifestations of functional adaptation. Functional adaptation, however, implies that the part involved adapts itself to new functional demands and actually fulfills the functions demanded. These endocardial pockets only

resemble pockets of the aortic valve. Even though they are brought about by the force of the blood stream and are often multiple, they can have no function (Karsner, 1955) because they are small, and hold only an insignificant amount of blood. To fulfill a function, it would be necessary that many be present, that they be large and close enough to each other to allow their cusps to touch, during diastole, as aortic cusps do. This, of course, holds only for diastolic pockets in aortic insufficiency.

Systolic pockets cannot possibly be interpreted as having any function whatever.

SUBAORTIC STENOSIS

There is perhaps a relationship between endocardial sclerosis, systolic pockets found on the endocardium of the interventricular septum just beneath the aortic valve, and the so-called "subaortic stenosis" of the left ventricle (Figure X-42). Some reviewers (see Gruenwald, 1947) of cardiac malformations mention the occurrence of subaortic stenosis in the outflow tract of the left ventricle and classify it as a congenital abnormality ("congenital subaortic stenosis"). While it is true that subaortic stenosis has repeatedly been found in association with malformations of the heart, this is not the rule and did not hold for *8 such instances described by Gruenwald*. In subaortic stenosis the endocardium covering the aortic outflow tract, at a varying distance below the valve, is diffusely thickened and gray-white. The thickening is often semi-circular and projects into the ventricular cavity, causing stenosis of the aortic outflow tract. Frequently (and in all instances reported by Gruenwald), the lower border of the thickened endocardium is more or less sharply defined and partly undermined, forming one or several pockets with openings directed toward the apex (systolic pockets).

Gruenwald concluded that subaortic stenosis may constitute a primary maldevelopment and may be the result of a fetal inflammation (see page 758) with subsequent congenital abnormality, or may have a postnatal origin. With regard to a primary maldevelopment, no compelling embryologic explanation of such a malformation has

yet been given, though Keith thought it might represent a remnant of the bulbus cordis. With regard to possible fetal inflammation, it will be



Figure X-42. Subaortic stenosis. Note fibrosis of endocardium beneath patent interventricular septum of pars membranacea, with systolic pockets.

recalled that Gross (1941) presented sufficient evidence to refute congenital inflammation as the cause of endocardial fibrosis.

Many instances of reported subaortic stenosis are associated with lesions in the aortic valve, causing stenosis of its orifice, or hypertrophy and dilatation of the heart from other causes, which may lead to a relative stenosis of the aortic conus. Two of Gruenwald's hearts disclosed obvious stenosis of the aortic orifice (rheumatic); another heart, "slight fusion of two cusps of the aortic valve." If there is fusion of two cusps, the circumference of the valve orifice must be narrowed and stenosis is present. Another heart had "arteriosclerosis" of the aortic valve with calcific plaques, and still another was "severely hypertrophic and dilated." Thus, it is clear that some hearts with subaortic stenosis also show lesions which may give rise to circumscribed endocardial fibrosis (sclerosis), with subsequent formation of systolic endocardial

pockets. In all of Gruenwald's 6 patients, the heart showed, not only subaortic stenosis, *i.e.*, annular or arched circumscribed endocardial sclerosis, but also systolic pockets. Thus, it would seem at least possible, if not probable, that subaortic stenosis is an exaggerated, circumscribed, endocardial sclerosis, caused either by mechanical trauma (Sternberg, 1930) or, rarely, by mural inflammation with secondary formation of systolic pockets. It should not always be classed with congenital malformations of the heart. On the other hand, it is conceivable that certain malformations, such as bicuspid aortic valve and coarctation of the aorta (Enzer, 1927), may provoke a functional abnormality or stenosis of the aortic conus which, in turn, causes subaortic circumscribed endocardial fibrosis (stenosis) with secondary formation of systolic pockets. So-called subaortic stenosis may also be complicated by what has been interpreted as subacute bacterial endocarditis or by acute bacterial endocarditis (Walsh *et al.*, 1943).

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Nonrheumatic Inflammatory Diseases of the Heart C. Myocarditis

By OTTO SAPHIR

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DIAGNOSIS OF MYOCARDITIS

FORMERLY when myocardial fibrosis, the result of coronary artery disease, was not distinguished from primary inflammatory disease of the myocardium, "chronic myocarditis" was diagnosed often and was an accepted cause of death on official death certificates. After the morphologists had convinced the clinicians of the advisability of limiting this term to conditions showing evidence of true primary inflammation of the myocardium, myocarditis became a rare diagnosis. Because of renewed interest in the myocardium in a number of infectious diseases and careful morphologic studies of the myocardium, the pathologist now recognizes that true myocarditis is not a rare disease; that it may develop in most bacterial and many virus diseases; that occasionally it may appear as a special, perhaps primary, disease

entity; and that it may cause death. In the light of these anatomic studies, the clinical diagnosis of myocarditis is now being made with increasing frequency.

In this chapter, myocarditis in general will be discussed principally from an etiologic point of view. For a review of the older literature, consult Monckeberg (1924) and Kirch (1927).

Incidence. Few references are available regarding the incidence of myocarditis.

Marcus (1947) reported 36 instances of non-specific myocarditis among 3800 autopsies. The diagnosis was based on the microscopic examination of routine sections, and on the average, only 2 blocks were cut in each case. He excluded rheumatic heart disease, bacterial endocarditis, acute pericarditis, pyemic abscesses in the myocardium, specific granulomas and specific infections that are known to cause myocardial lesions,

such as diphtheria and scarlet fever. Brown and Hunt (1940) found acute myocarditis microscopically in 58 hearts from 625 routine consecutive autopsies. Albert (1938) studied the hearts of 113 children with various acute infectious diseases and noted myocarditis in 40. At Michael Reese Hospital, among 5626 autopsies from which routine histologic sections were examined (Saphir, 1942a), myocarditis was found 240 times (4.3 per cent). Among 1000 other consecutive autopsies at the same institution, when more than the usual number of blocks (about 25) were taken from each heart for microscopic section (unpublished study), myocarditis was observed 90 times (9.0 per cent). A total of 1402 cases of myocarditis was reported from the Armed Forces Institute of Pathology by Gore and Saphir (1948). As Moritz and Zamcheck (1946) stated, the total number of autopsies recorded at the Armed Forces Institute of Pathology between January, 1942 and January, 1946, when practically all of these 1402 cases were observed, amounted to more than 40,000. Of the 1402 hearts, 130 had rheumatic disease, while more than 90 per cent were nonrheumatic.

Table X-15, taken from Gore and Saphir, indicates the frequency of myocarditis in association with various diseases and clinical conditions.

Blankenhorn and Gall (1956) found 108 cases of "myocarditis" among 3141 autopsies (3.4 per cent). However, in 31 of these 108 cases the diagnosis was "myocardosis." This term is now used more often than formerly (Wuhrmann, 1950) to denote degenerative lesions of the myocardial fibers rather than true inflammation. It is usually thought that clinically myocardosis cannot be distinguished from myocarditis. The suffix, *osis*, indicates either "a state of" or "increase in production" (Jaeger, 1950). However, because the latter meaning is so often employed, we do not recommend use of the suffix, *osis*, to denote degenerative changes.

Age Distribution. Among the 90 instances of myocarditis mentioned above, which were found in 1000 consecutive autopsies, only eight were associated with endocarditis. The age distribution was as follows:

Age in Years	Number of Cases
Less than 1	3
1-10	12
11-20	3

21-30	8
31-40	11
41-50	12
51-60	10
61-70	20
71-80	8
81-90	3

It is interesting that 31 instances were encountered in the age group from 61 to 90 years, an age period in which myocardial changes resulting from vascular disease are extremely common. There were 47 males and 43 females. Among Marcuse's (1947) 30 patients, 20 were males (72 per cent) and 10 females; the percentage of males in his entire autopsy material of 3800 cases was 65. The ages of these patients ranged from 1 month to 80 years. Twenty-two patients were below the age of 40, and 8 of these were less than 15 years old.

Unexpected Death from Myocarditis. There are a number of communications on record stressing unexpected deaths from myocarditis.

Wuhrmann (1939), in his monograph, commented on unexpected deaths in patients with myocarditis. Among 90 patients studied by Saphir and co-workers (1944) 9 had died unexpectedly. Single instances of unexpected death have been reported by Helwig and Wilhelmy (1939), Coulter and Marcuse (1944), and many others. Moritz and Zamcheck (1940) reported death from acute heart failure in 14 soldiers with acute and subacute (isolated) myocarditis; 10 of the 14 died within a few minutes after an unexpected syncopal attack. Glatthar (1946) expressed the belief that foci of inflammation around vital branches of the coronary arteries or within the conduction system may be responsible for cardiac symptoms as well as for electrocardiographic changes and occasionally also for sudden death. Boemke (1948) found that, among 1816 German soldiers who died suddenly in World War II, myocarditis was responsible in about 5 per cent.

CLASSIFICATION

Brown and Hunt (1940) classified myocarditis as acute, syphilitic and tuberculous. Acute myocarditis was subdivided into non-specific and rheumatic types.

Marshall (1942) classified infective myocardial disease into (1) specific myocarditis (rheumatic fever, tuberculosis, gumma); (2) nonspecific,

TABLE X-15
Associated Disease or Clinical Condition in 1042 Cases of Myocarditis*
(From Gore and Saphir, 1947a)

	Column 1	Column 2		Column 1	Column 2
Rickettsial diseases	227	227	Septicemia	11	23
Scrub typhus	23	48	Streptococcal	34	107
Epidemic typhus	9	19	Staphylococcal	9	18
Rocky Mountain spotted fever	144	221	Pneumococcal	15	Unknown
Other acute bacteremias	208	208			
Diphtheria	130	130	Acute glomerulonephritis	14	160
Subacute bacterial endocarditis	111	256	Acute tonsillitis	12	Unknown
Rheumatic heart disease	24	44	Acute nasopharyngitis	41	Unknown
Meningococemia	7	8	Cellulitis, lymphangitis, and wound infections	13	Unknown
Scarlet fever	6	11	Tularemia	1	16
Well's disease	2	66	Brucellosis	2	4
Relapsing fever	1	1	Miscellaneous (postinfectious)	13	Unknown
Syphilis (gummatous)	5	41	Exfoliative dermatitis	7	44
Chagas' disease	5	135	Arenical reaction	1	18
Schistosomiasis	2	2	Sulfonamide hypersensitivity	105	Unknown
Malaria	13	144	Disease unknown (so-called "idiopathic")	43	Unknown
Trichinosis	13	94	Starvation	33	50
Acute encephalitis	6	9	Heat stroke		
Polioomyelitis	3	30	Surviving less than 24 hours	16	45
Infectious mononucleosis	1	8	Surviving more than 24 hours	13	26
Gaillain-Barre' syndrome	1	400	Carbon monoxide poisoning	1	30
Mumps	1	9	(limited to patients who survived for an appreciable interval after the fatal exposure)		
Epidemic hepatitis	32	222	Following medication with Emetine	1	70
Snailpox	9	581	Burns	11	45
Virus pneumonia	3	12			
Tuberculosis	9	48			
Bock's saroid	3	5			
Coccidioidomycosis	11	9			
Blastomycosis	2	6			
Actinomycosis	1				
Torulosis	1				
			Total	1402	

* The figures in the first column represent the number of times myocarditis was encountered. Wherever possible, the number of cases of each disease, screened to ascertain the first figure, is given in Column 2. The ratio of the two thus provides a crude index of the frequency of myocarditis in each disease.

toxic (diphtheria and other fevers); (3) septic; and (4) isolated myocarditis. Candel and Wheelock (1945) classified infectious myocarditis as (1) specific myocarditis (rheumatic fever, tuberculosis, syphilis), (2) nonspecific myocarditis (a) of known etiology, as diphtheria, tonsillitis, typhus, bronchiectasis, or clinical entity of undetermined etiology, such as infectious mononucleosis, (b) of unknown etiology (Fiedler's myocarditis); and (3) septic myocarditis (septicemia and associated subacute bacterial endocarditis).

Lustok and associates (1955) classified myocarditis as acute, recurrent, or chronic. The acute form is either fulminating, with sudden onset and fatal termination, or benign. The benign form may be symptomatic or asymptomatic, in the latter case, it may be discovered by electrocardiographic or roentgenographic examination.

For didactic purposes, a classification of myocarditis is presented in Table X-16.

TABLE X-16

Classification of Myocarditis

"Fetal myocarditis"

Myocarditis following infectious and contagious diseases (as bacterial, virus, fungous, helminthic)

With endocarditis

Without endocarditis

Isolated myocarditis

Diffuse (sometimes the result of hypersensitivity)

Granulomatous (cause as yet unknown)

Specific myocarditis*

The defect in such a classification is immediately obvious. It is not free from the criticism of overlapping. Thus, gonococcal and meningococcal myocarditis may or may not be associated with endocarditis; and rheumatic myocarditis may be classified as a specific myocarditis or as a form of myocarditis that may follow endocarditis.

The above classification is in part etiologic. Jaffé (1944) believed that such a classification in relation to accompanying infection was valuable clinically but rather unsatisfactory pathogenetically. He suggested that in the light of genesis only two groups of myocarditis can be distinguished: (1) those in which the organisms are actually present in

the myocardium and produce tissue reactions; such cases include myocarditis of septicemia, tuberculosis, and gunnias; and (2) those in which the myocardium is free from the organisms but is indirectly influenced by the organisms at distant sites, as in diphtheria.

Jaffé often remarked that myocarditis occurs frequently. Thus, in 5000 autopsies performed in Venezuela, he encountered 500 cases of myocarditis (1946). Most of these disclosed the same histologic picture. He emphasized that only the muscle damage is a direct consequence of the underlying disease. This damage may be caused by various extrinsic agents, such as bacteria or parasites, or by intrinsic agents, as in metabolic disturbances. He further stated that it is a tenable assumption that the body may react similarly to various causes, especially if the etiologic agent affects the parenchymatous cells or organs, and if these damaged cells produce further reaction as a result of faulty secretion and absorption of products of cellular disintegration. Furthermore, in many illnesses the pathologic process may be the result, not of a single transitory insult, but often of continued and repeated insults. Thus, another factor is added, namely, the allergic reaction of the individual, which in itself gives rise to various tissue changes. He concluded that chronic myocarditis is to be regarded as a uniform process in which there is, primarily, damage to the cardiac muscle fibers and, secondarily, mesenchymal alterations with cellular infiltrations. This process, although purely inflammatory, must be distinguished from all those myocardial inflammations in which organisms are present *in situ*; it is the result of the allergic reaction of the previously damaged cardiac muscle.

This concept of myocarditis will be further discussed in relation to isolated myocarditis. It may be mentioned here that so-called allergic myocarditis or myocarditis in hypersensitivity presents microscopically a more or less well-defined entity (Rich and Gregory, 1943a and b; French, 1946) which often is quite characteristic microscopically, and which does not always conform to Jaffé's description.

FETAL MYOCARDITIS

Reports of fetal (congenital) myocarditis, except in congenital syphilis, are exceedingly rare. Such reports are found chiefly in the older literature (Abbott, 1926) and usually are concerned with myocardial changes in

* "Specific" indicates changes which histologically are so characteristic that a diagnosis of the cause can be made from the morphologic picture alone without recourse to bacteriologic studies, e.g., rheumatic, tuberculous, syphilitic (gummatous).

hearts showing congenital anomalies. Gross (1941) stated that the valvular changes in so-called congenital endocarditis (see page 759) are not the result of inflammation, but signify the persistence of an early developmental stage of the involved valve. He also added that myocardial lesions seen in such hearts are not inflammatory in origin but represent healed, bland infarcts. Saphir and associates (1944), in studying 78 congenital anomalies of various types, exclusive of minor anomalies such as a patent foramen ovale and patent ductus arteriosus, found an increase in connective tissue in several hearts but no inflammation, either acute or chronic.

It is known that many children with severe congenital cardiac anomalies get along fairly well, though occasionally one may die unexpectedly. Intriguing as it may be to assume that myocardial changes are the direct cause of death in these children, a careful histologic study of such hearts usually discloses no evidence of any anatomic lesions in the myocardium to which death can be attributed.

One rather unusual instance was reported by Monson (1948), in which a child with tetralogy of Fallot died during a short-circuiting operation. At autopsy, death was attributed to myocarditis. Froboese (1932) found severe myocardial fibrosis in a 6-month-old infant, which he interpreted to be the result of a congenital myocarditis (fibrosis myocardi congenita). There were no congenital anomalies.

A number of examples of myocarditis have been reported in newborn infants, which were thought to have been caused by a maternal infection with Coxsackie virus (Javett *et al.*, 1956). See also page 810.

Recorded instances in the literature of so-called idiopathic enlargement of the heart are definitely not the result of inflammatory changes of the myocardium. Some of these have been found associated with "status thymicolymphaticus" while others are classified as glycogen infiltration (von Gierke's disease). (See also fibroelastosis.)

From a review of the literature and from studies of the myocardium of a number of hearts with congenital anomalies observed in this laboratory, it must be concluded that (with the exception of myocarditis in congenital syphilis) fetal or congenital myocarditis, if it occurs at all, is extremely rare.

MYOCARDITIS IN INFECTIOUS DISEASES

Acute Nasopharyngitis and Acute Tonsillitis. The literature contains reports of myocardial damage resulting from tonsillitis. Most of these, however, are clinical, some presenting changes in the electrocardiogram as evidence of myocardial damage.

Wuhrmann (1939) regarded chronic tonsillitis as a type of infection that may be responsible for myocarditis. Scherf and Boyd (1939) emphasized repeatedly that commonly focal infections, such as those of chronic tonsillar infection, cause myocarditis. Scherf (1940) reported 5 nonfatal cases in which myocarditis followed acute tonsillitis. He stated that in his experience this complication occurred in 10 to 15 per cent of such cases. Candel and Wheelock (1945) mentioned a patient with peritonsillar abscess in their series of nonfatal cases and described 1 fatal case with autopsy in which myocarditis followed acute tonsillitis.

In a study of the pertinent material available

at the Armed Forces Institute of Pathology, reported by Gore and Saphir (1947b), there were 35 instances of nonrheumatic myocarditis in association with upper respiratory infections. The portal of entry in 12 of these was acute tonsillitis and in 23, acute nasopharyngitis. Septicemia was not believed to be of etiologic importance, since significant visceral alterations were absent in all 35 cases. *Corynebacterium diphtheriae* was absent from the culture material and diphtheria had been excluded clinically in each instance. The cause of death was cardiac failure in all cases. Fifteen of the patients had died unexpectedly. Grossly the hearts were soft, flabby and friable, and the myocardium was pale, gray or streaked with gray, or mottled with red or yellow. Petechial hemorrhages were found subepicardially 7 times and diffusely scattered throughout the myocardium 3 times; mural ventricular thrombi were encountered in 1 case, and 5 hearts were regarded as grossly normal.

Histologically, the inflammatory cellular response was predominantly and characteristically

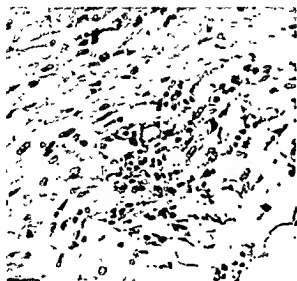


Figure X-43 Myocarditis in patient with organizing pneumonia. Note the many monocyte cells, eosinophilic granules. Hematoxylin X 300

nonnuclear. In the most cellular zones, lymphocytes outnumbered the other elements which included mononuclear cells larger than lymphocytes with densely stained nuclei, polymorphonuclear leukocytes and Aschoff cells. Aschoff cells, though they constitute parts of the Aschoff body, are often found in various types of myocarditis and *per se* are neither characteristic of any specific lesion nor are they pathognomonic of rheumatic fever. They are characterized by an undant, faintly basophilic cytoplasm, a lightly stained oval nucleus, a thin sharp nuclear membrane and a characteristic arrangement of the chromatin in the form of a central bar or node in which weblike processes extend toward the periphery. Aschoff cells are also known as "myocytes," because of Anitschkow's (1913) original interpretation, and as myocardial reticulocytes (Erlich and Lapan, 1939).

Endothelial leukocytes (histiocytes) and Aschoff cells were frequently found in small accumulations about a few intensely acidophilic, homogeneous muscle fibers, and sometimes infiltrated the interstitial tissues more diffusely, especially perivascularly about the orifices of the coronary vessels. The focal cellular accumulations around a few necrotic muscle fibers appeared to present a very early and rapid morphologic change which Gore and Saphir termed an "exosive lesion." Plasma cells and eosinophils were found in varying numbers, and in older lesions fibroblasts were observed. Mast cells were present, as they are normally, but apparently they did not participate to any extent in the inflamma-

tory reaction. Bacteria were absent from all sections examined. The inflammatory cells were accompanied by exudation of variable quantities of protein-rich fluid in the interstitial tissue. Lustok and associates (1955) reported that 13 of their 45 patients with myocarditis gave a history of acute respiratory infection. In the series of Bengtsson and associates (1951), the incidence of myocarditis among 798 patients with acute hemorrhagic tonsillitis, on the basis of clinical observations, was 3.9 per cent.

It is thus evident that myocarditis is occasionally associated with acute nasopharyngitis, acute tonsillitis, and infections of the upper respiratory tract in general. Yet, reported autopsy cases are exceedingly rare; Candel and Wheelock (1945) believed that their report of acute nonspecific myocarditis following acute tonsillitis was the first recorded case proved by autopsy.

Pneumonia. Relatively few references are found in modern literature to myocarditis in pneumonia.

Stone (1922) examined microscopic sections of the myocardium in 34 cases of lobar pneumonia and 37 cases of bronchopneumonia. Polymorphonuclear leukocytic and round cell infiltrations were found in 8.9 per cent, and outspoken interstitial myocarditis in 2.9 per cent of the patients with lobar pneumonia. Among the patients with bronchopneumonia, polymorphonuclear leukocytic and round cell infiltrations occurred in 10.8 per cent and interstitial myocarditis in 2.7 per cent. Newkoff (1914), Liebmann (1915), Berry (1920), Roesler and Soloff (1935), Swift and Smith (1937), and Spuhler (1942) reported isolated instances of myocarditis in pneumonia. Saphir and Anromin (1948) studied 67 hearts of patients with bronchopneumonia in whom the inflammation of the lung had involved at least one entire lobe. Twenty-six or 38.8 per cent of these revealed inflammatory changes sufficient to warrant the term "myocarditis" (Figure X-43); 15 of the 26 were classified as acute myocarditis, 3 as acute serous, and 8 as subacute myocarditis. The outstanding clinical criteria pointing to the diagnosis were found to be: disproportion between the pulse rate and the temperature, drop in the arterial blood pressure, cyanosis out of proportion to the apparent pulmonary involvement, and unexpected death. Six of these 26 patients exhibited electrocardiographic abnormalities. The authors emphasized the necessity of examining multiple sections of the myocardium

either to establish or to disprove a diagnosis of myocarditis. Among 240 instances of myocarditis studied by Saphir (1942a), myocarditis was found in association with lobar pneumonia 7 times, and with bronchopneumonia 19 times.

Myocarditis is also occasionally encountered in so-called acute *laryngotracheobronchitis*. Saphir (1945a) reported unexpected death in 5 children. The autopsies disclosed severe laryngeal edema and edema of the epiglottis and subglottis, with absence of any obstructing (pseudo)membrane. Grossly, the hearts were dilated, and microscopically the myocarditis was principally interstitial in distribution. The most commonly encountered inflammatory cell was the lymphocyte. Neutrophils were rarely present. Three of these 5 instances disclosed, on microscopic examination, early bronchopneumonia which was not recognized grossly.

Fatal myocarditis also occurs in *bronchiectasis*. Jex-Blake (1920) mentioned that 3 of 110 patients with bronchiectasis died of heart failure. He apparently referred to right ventricular hypertrophy with ultimate right heart failure. Ogilvie (1941) stated that myocardial damage occurs as a late result of chronic sepsis. Claflee and associates (1942) described myocarditis in a patient who died suddenly after an asthmatic attack. The myocardium was massively infiltrated with eosinophils, polymorphonuclear leukocytes, a few lymphocytes, and plasma cells, and also contained small foci of necrosis. Bronchiectasis was found in 152 of 6257 autopsies (Saphir, 1943). Myocarditis was encountered in 8 of these 152 autopsies. In 3 the myocarditis was recent, but complicated by myocardial fibrosis in 1 of the cases, and associated with an aneurysm of the heart in another. Subacute myocarditis and true chronic myocarditis were each present twice. Three of these 8 patients had died unexpectedly.

Whooping Cough (Pertussis). The older literature includes whooping cough as a causative factor in myocarditis (Kirch, 1927).

Oberndorfer (1914) demonstrated myocarditis in a 7-year-old girl who died unexpectedly a few weeks after having contracted whooping cough. There were many infiltrations of round cells throughout the myocardium. Among 27 instances of myocarditis reported by Vischer (1924), 1 patient with whooping cough had an interstitial myocarditis with predominating lymphocytes and a few leukocytes and plasma-like cells. Brick (1913) studied microscopically the hearts of 7

patients with whooping cough. In 1 (Case 7), a few leukocytes and small accumulations of round cells were present; in another (Case 12), occasional leukocytes were encountered throughout the myocardium. In general, hypertrophy of the right ventricle was the main cardiac abnormality.

Influenza. Myocarditis from virus infection will be discussed later. The literature contains a number of instances in which myocarditis was thought to have been the result of infection with *Haemophilus influenzae* or of infections loosely called "flu" or "grippe." A number of these reports are not detailed enough to warrant the conclusion that the myocarditis had been caused by a definite organism.

Of 27 persons with fatal influenza (virus infection?) in the epidemic at Camp Devens in 1918, reported by Wolbach and Frothingham (1923), the myocardium of only 1 revealed small areas of cellular infiltration, consisting chiefly of mononuclear cells with a few polymorphonuclear leukocytes and mast cells. Schmorl, according to Kirch (1927), was the first to refer to myocarditis in patients dying during the epidemic of "grippe" in Europe in 1918. Miller and Branch (1923), and DeSanto and White (1933) described myocardial changes in a *Haemophilus haemolyticus* infection. Lichty (1937) found myocarditis caused by a hemolytic parainfluenza bacillus. Craven and associates (1940) reported myocarditis in 2 instances of endocarditis caused by *Haemophilus parainfluenzae*.

Diphtheria. Myocardial damage is a well-known and sometimes fatal complication of diphtheria. The literature up to 1940 has been reviewed by Saphir (1942).



Figure X-44. True chronic myocarditis. Note the fibrosis associated with the inflammatory cells. Iron-hematoxylin. X 250.



Figure X-45 (left). Early hyaline necrosis of myocardium in diphtheria. Section is from the heart of a guinea pig that died 27 hours after intraperitoneal injection of virulent culture of *Corynebacterium diphtheriae*. Hematoxylin and eosin. X 450. (WCGH, 40 P 379.)

Figure X-46 (right). Hyaline necrosis of myocardium in diphtheria. Patient died 14 days after onset of pharyngitis. Note absence of true inflammation. Hematoxylin and eosin. X 150. (WCGH, 45 P 191 L.)

Ch'in and Huang (1941) gave a general review of the histologic lesions of the myocardium in diphtheria. Warthin (1924) presented an analysis of the findings in 17 diphtheritic hearts, stating that the essential lesion was toxic parenchymatous hyaline degeneration or necrosis (Figures X-45 and 46), often with fatty infiltration. He indicated that a reparative inflammatory process (myocarditis) develops later. Whether the term "myocarditis" is justified, in speaking of a reparative inflammation, is questionable. Unfortunately, other investigators have used the term myocarditis, not to denote simple reparative inflammation, but to signify a primary myocardial inflammation in diphtheria. Nuzum (1919) described an eosinophilic myocarditis in diphtheria.

Gore (1948) reported the findings from autopsy records and microscopic slides of 221 fatal cases of diphtheria, of which 205 were available for study. Myocarditis alone was encountered in 99 instances. Myocarditis with neuritis was reported 44 times, the presence of neuritis being determined solely from the clinical records, whereas the diagnosis of myocarditis was based on microscopic findings. Gross cardiac abnormalities were reported in 71 per cent of the cases. Dilatation of the chambers, flaccidity, pallor, and "streakiness" of the myocardium, noted singly or in combina-

tion, were the changes most frequently reported. The extent of the microscopic changes varied from severe involvement with large and multiple areas of muscle damage to minor changes with only occasional small foci of involvement. No organisms were demonstrable microscopically in any of the sections examined. Gore emphasized that the diphtheritic infection produces a varying degree of parenchymal damage, manifested as segmental hyaline, granular and fatty degeneration of the muscle fibers. The secondary inflammatory response of the stroma appears, at first, to consist largely of locally developed histiocytes, but it is soon augmented by an influx of plasma cells and lymphocytes. Degenerated muscle is destroyed, leaving gaps and defects in the myocardium which, if the length of survival permits, heal by fibrosis (Figure X-47). The muscle showed only abortive regeneration. Statements by Anitschkow (1913), Heller (1914) and Warthin (1924) to the effect that there is true muscle regeneration were based on Anitschkow's belief in the myogenic character of the "myocyte," a cell now generally regarded as a histiocyte. In one-third of the cases, the manifestations of myocarditis appeared at a time when the patient seemed to be well on the way to convalescence. The interval between clinical manifestation of

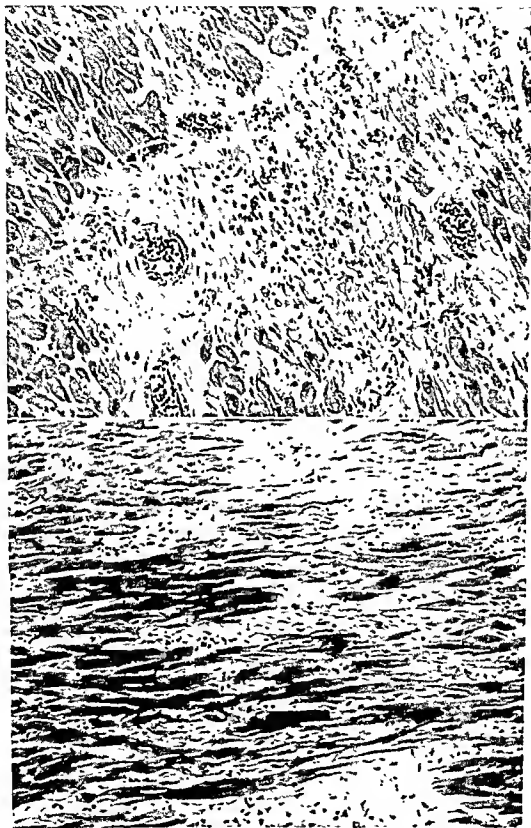


Figure X-47 (*upper*). Myocardium in diphtheria. Area of necrosis is being organized and replaced by young fibrous tissue. X 125. (Courtesy of Armed Forces Institute of Pathology. Acc. 152,452.)

Figure X-48 (*lower*). Healing of areas of myocardial necrosis in diphtheria, with early fibrosis. X 90. (Courtesy of Armed Forces Institute of Pathology. Acc. 143,672.)

diphtheria and the onset of cardiac symptoms has been designated as "the deceptive interval" of apparent improvement.

Greene (1946) believed that the myocardial changes in his case were caused by a combination of sulfonamides and diphtheria toxin. He thought that cloudy swelling, simple necrosis, and granular fragmentation were characteristic of myocardial involvement in diphtheria, and that the interstitial reaction, the round cell and polymorphonuclear leukocyte infiltrations and the fibroblastic proliferation were secondary. On the other hand, the presence of large pale mononuclear cells with eosinophilic cytoplasm was believed to be representative of sulfonamide medication. He concluded that the usual hazards of sulfonamide therapy are increased when the heart is already damaged by diphtheria or other toxins.

Myocarditis has also been reported as a complication of cutaneous diphtheria (Solomon and Irwin, 1947).

Kay and Livingood (1946) found evidence of myocarditis in 4 patients among 140 with cutaneous diphtheria, 1 of the 4 died. These authors were impressed with a definite parallel relationship between the severity of the cutaneous lesions and development of cardiac complications.

As a result of the myocardial changes in diphtheria, fibrosis and hyalinization may ensue (Figure X-48). Occasionally, instances of calcification of the heart muscle fibers have been reported.

Ceelen (1919) stated that the toxin of *Corynebacterium diphtheriae* may produce parenchymatous degeneration and, at times, even calcification of the myocardium. He observed partial calcification of the fibers of the right bundle branch and also calcification within the myocardium. Kratzseisen (1920) noted deposition of calcium within the diseased muscle fibers of the heart of a patient who died of diphtheria. Edelstein (1946) observed massive calcification with ossification in the myocardium of an 11-year-old boy. Though no definite etiology for this lesion was evident, it seemed that either diphtheria or infection with *Haemophilus influenzae* produced degenerative changes and necrotizing lesions of the heart muscle with secondary calcification. The heart was the only organ in the body which showed calcification.

Heart block is often encountered in diphtheria. Only Kocher's study (1947) will be mentioned here. At autopsy, he found, in a diphtheritic patient with complete heart block, diffuse destruction of muscle fibers within the interventricular septum. These fibers were surrounded by infiltrations of neutrophils, lymphocytes, monocytes and a few plasma cells; the process had extended into the junctional tissues between the atrium and ventricle.

Also on record are a number of reports of myocardial changes in experimental animals injected with toxins of *C. diphtheriae*. Cukelberger (1936) produced myocardial lesions in 24 of 28 guinea pigs by injecting diphtheria toxins (0.0006 Gm. per 100 Gm. of body weight).

Sayers (1958) observed a patient who, 12 years previously, had had a severe attack of diphtheria with myocardial involvement, and then developed myocardial insufficiency, and finally died in congestive heart failure at the age of 41. Grossly the myocardium showed no changes but, microscopically, some sections had large areas of fibrosis and other sections had fine strands of fibrous tissue situated between myocardial fibers.

Scarlet Fever. Stoeber (1935) examined the hearts of 22 patients who died of scarlet fever. The ages ranged from 5 months to 28 years, except for one patient who was 50 years old. Six hearts had no microscopic changes, and in 4 the changes were minute. The other hearts disclosed various amounts of cellular infiltration. Particularly prominent were faintly-stained large oval cells without recognizable cytoplasm and large nuclei which showed fine ramification of the chromatin. These cells were obviously Aschoff cells. Hemorrhages in the conduction system may be the cause of unexpected death in scarlet fever. Stoeber also remarked that the same patient may have scarlet fever and rheumatic fever and both types of myocarditis. The latter remark is interesting and recalls Schmorl's findings (1914) of typical Aschoff bodies in the heart of a 2-year-old child who died of scarlatinal myocarditis.

Fahr (1921), apparently stimulated by Schmorl's statement, studied the hearts of 9 patients who died as a result of scarlet fever. In 4 patients the diagnosis of myocarditis had been made clinically. In not a single instance were

rheumatic nodules (Aschoff bodies) found in the myocardium. However, minute granulomata were present, particularly around the small blood vessels. These nodules were much smaller than Aschoff bodies and no giant cells were seen. Four of the 9 hearts also had endothelial cell proliferation of the endocardium in the form of small nodules. In 3 other hearts only a few such nodules were found, and in 2 they were absent. Kirch (1927), discussing Fahr's studies, concluded that the rheumatic nodules (Aschoff bodies) are specific lesions, occurring in no other disease, and must be well separated from the nodules seen in scarlet fever. Fahr (1930), a few years later, studied the heart in 11 cases of scarlet fever, and in 1 instance found a severe myocarditis. The most commonly encountered change was subendocardial proliferation in the form of minute nodules.

Magladery and Billings (1936) emphasized the difference in intensity of myocardial involvement in various epidemics of scarlet fever. Among 37 cases of scarlet fever, they found 29 with myocarditis which sometimes was of mild degree. However, by using the oxidase reaction, they clearly demonstrated an increase of granulocytes. In 1 heart, they encountered perivascular infiltrations which resembled Aschoff bodies, this heart also had acute verrucous endocarditis.

Brody and Smith (1936) studied the visceral lesions in scarlet fever and related streptococcal infections; in a series of 44 patients with scarlet fever and of 15 patients with possible scarlet fever the hearts were examined microscopically. They stated that lesions of varying severity occurred in over 90 per cent of the hearts, the chief cell being some form of round cell. These lesions fell into three overlapping types: (1) either a focal or a diffuse interstitial infiltration of the myocardium, having no apparent distribution with reference to the cardiac blood vessels and usually seen in conjunction with either of the following two types; (2) an infiltration, either in or about the smaller coronary arteries (arteritis or periarteritis), in which the invading cells were mononuclear, although in some cases there was a slight admixture of neutrophilic polymorphonuclears and rarely eosinophils; (3) the commonest type, consisting of a subendothelial infiltration which sometimes occurred beneath the endocardium of the ventricular chambers but was most striking in the walls of the thebesian vessels. On the basis of clinical observations, Bengtsson and associates (1951) diagnosed myocarditis in 3.9 per cent of 3069 patients with scarlet fever.

In summary, it seems that myocarditis not rarely is associated with scarlet fever. The inflammation is characterized principally by involvement of the interstitial tissue, although the cardiac muscle fibers may be replaced by inflammatory cells. The cells most commonly encountered are lymphocytes which may be distributed perivascularly in the form of minute nodules. Circumscribed proliferations of endothelial cells are encountered relatively often in subendocardial regions.

Meningococcal Infections. To judge from the relevant literature, myocarditis is rarely caused by meningococci. Case reports of meningococcal endocarditis disclose an accompanying myocarditis more often than might be expected. Reports of meningococcal myocarditis in the absence of endocarditis, however, are quite rare, possibly because the myocardium is not carefully enough examined.

Saphir (1936) examined the heart in 10 instances of meningococcemia and reported myocarditis in 2. The myocarditis was characterized by hemorrhagic exudate with the presence of endothelial leukocytes and a few polymorphonuclear leukocytes, some of which contained gram-negative diplococci. Ferguson and Chapman (1948) examined the heart in 16 cases of acute fulminating meningococcal infections and described inflammatory cells in the myocardium in 12. The inflammatory exudate consisted of varying numbers of mononuclear leukocytes; in addition, occasional foci of necrosis were encountered. Epstein and associates (1947) also wrote on meningococcal myocarditis.

Montz and Zamcheck (1946) studied 350 cases of fatal meningococcal infections reported by the Armed Forces Institute of Pathology. In 110 of these patients death occurred within 24 hours after the onset of incapacitating symptoms. Myocarditis (myocardial exudation) was observed in 37. In 14 instances postmortem examinations disclosed no significant pathologic changes other than myocarditis. It is apparent from the histologic studies of these hearts that the diagnosis of myocarditis usually referred to an exudation of polymorphonuclear leukocytes superimposed on a monocytic reaction which might be focal or diffuse, and sparse or dense.

It is well known that patients with men-

ingococcemia having the so-called *Waterhouse-Friderichsen syndrome* may die unexpectedly. No pertinent references are found in the literature to the association of meningococcal myocarditis with this syndrome. However, when reports of Waterhouse-Friderichsen syndrome are scrutinized, it is found that myocarditis is sometimes described even though such reports do not include "myocarditis" in their titles. (See Saphir, 1949.) Because there are few references in the literature to myocarditis in the Waterhouse-Friderichsen syndrome, the following significant cases will be quoted.

In an instance of the Waterhouse-Friderichsen syndrome, Herbut and Manges (1943) found, immediately beneath the endocardium of the left ventricle, several sharply circumscribed hemorrhages which microscopically were composed of normal and laked erythrocytes. Occasionally the capillary walls and the immediately adjacent connective tissue were permeated with polymorphonuclear leukocytes. Small collections of polymorphonuclear leukocytes, dissociated from blood vessels, were also seen between the muscle fibers and in the supporting connective tissue. D'Agati and Marangoni (1945) studied the heart in 5 cases; in all 5 patients the microscopic changes were of a nonspecific character, similar to those found in other infectious diseases and in septicemias. Ikeda and Rosenthal (1945) reported 2 instances; in 1 they recognized a focal collection of polymorphonuclear leukocytes which, they stated, might lead one to suspect focal myocarditis. Newman (1945) recorded 3 instances of this syndrome. In the first, foci of neutrophilic leukocytes and a few large mononuclear cells were scattered widely through the myocardium, in a second case, the myocardium contained many polymorphonuclear leukocytes in the interstitium and a rare zone of myocardial necrosis. Holman and Angevine (1946) reported fulminating meningococcal septicemia in 2 patients, 1 having definite signs of circulatory collapse. One of these patients died and the autopsy disclosed widely disseminated areas of edema, capillary engorgement and degeneration of muscle fibers. The second patient survived, but electrocardiographic changes were noted. In a review of 29 autopsied cases of meningococcal infection, they stated that acute myocarditis was found microscopically in 7, and was associated with septicemia in 6 of these 7 patients.

Kinsman and associates (1946) stated that the cause of the circulatory collapse, which is such a prominent phenomenon in this disease, has been the subject of much speculation. It seems unreasonable to place the entire blame on the exhaustion of hormonal supply which is associated with the adrenal lesions, even though the latter are usually of high degree, as in the fatal cases reported here. In certain instances, injuries of other organs may be responsible to a greater or lesser degree. In one of their patients, there was pulmonary edema and bilateral hydrothorax, consistent with circulatory failure of cardiac origin. On microscopic examination of the heart, degeneration of muscle fibers and polymorphonuclear and mononuclear leukocytic infiltrations of the connective tissue were observed. It was believed that the myocardial changes were sufficient to have caused circulatory collapse. Wasserman (1946) stated that the viscera, aside from the adrenal glands, usually show no significant pathologic lesions, with the exception of acute cloudy swelling of the myocardium, the kidneys and the liver. Rappaport and Zuckerbrod (1945) reported a patient who had a fulminating meningococcal infection and stated that myocarditis had been proved by electrocardiography. Gormsen (1955) studied 3 cases of myocarditis in meningococcemia. In this connection, Black-Schaffer and associates (1947) were able to produce occasional foci of acute myocarditis and necrosis in experiments designed to determine whether a relationship exists between the lesions of meningococcal purpura and the Schwartzman phenomenon.

Saphir (1949) found myocarditis in 4 patients with Waterhouse-Friderichsen syndrome. Two of these patients were dead on arrival at the hospital and the other 2 died 4 and 7 hours, respectively, after admission. Hemorrhages in the skin and throughout both adrenals were found in all 4 patients.

It is important to note that at times myocarditis may be associated with meningococcal meningitis or meningococcemia, and that such associated myocarditis, with resulting myocardial failure, will seriously influence the prognosis in meningococcal meningitis, not only because of myocardial failure, but because the myocarditis is seemingly the result of an overwhelming infection with meningococci.

From a review of these case reports of

Waterhouse-Friderichsen syndrome, it thus appears that myocarditis has been occasionally noted as a complication. A fall of blood pressure, coincident with gallop rhythm, had been observed in 1 of these patients, and in another myocarditis was recognized clinically by means of electrocardiographic changes. Myocarditis, believed to have been sufficient to cause circulatory collapse, had been noted in a third instance.

Among the 97 instances of myocarditis in children studied by Saphir and co-workers (1944), there were 4 in which myocarditis was associated with meningitis. In 2, myocarditis and meningitis were caused by *Haemophilus influenzae*, in 1 by streptococci, and in another by pneumococci.

Gonococcal Myocarditis. Gonococcal myocarditis, in the absence of gonococcal endocarditis, is extremely rare; myocarditis, however, is often found in association with gonococcal endocarditis. Focal necrosis with abscesses seems to be the most commonly encountered lesion (Williams, 1938).

Sabathie (1935) stated that in some instances of gonococcal endocarditis, a primary abscess was found in the interatrial or interventricular septum and that the valves were involved secondarily. Bang (1940) remarked that the possibility exists that gonococcal myocarditis may be a cause of chronic cardiac disease. As Bang emphasized, in textbooks on heart disease, gonorrheal infection is rarely mentioned as a possible cause of myocarditis. In Candel and Wheelock's (1945) clinical report of patients with myocarditis, 3 had acute gonococcal arthritis.

Salmonella Infections. Myocarditis in these infections is rare, while degenerative changes, such as cloudy swelling and fatty degeneration, are reported more often.

Kirch (1927) stated that myocardial changes in typhoid fever are far less common than one is led to believe from the older literature. Munzer (1947) found, in 35 of 60 patients with typhoid fever, electrocardiographic abnormalities other than tachycardia and bradycardia. In 18 the changes persisted during convalescence and in 1 they first developed during this period. He described cloudy swelling or hyaline degeneration of myocardial fibers with necrotic foci of

minute size, and scattered or focal interstitial infiltrations. He concluded that myocarditis is the cause of death in typhoid fever more often than is suspected. At the peak of the infection, the myocarditis is easily overshadowed by the peripheral circulatory disturbance, the clinical manifestations of this myocarditis, tachycardia and circulatory instability after exercise, do not become manifest until convalescence and then persist for a longer time, in most cases, than the electrocardiographic alterations.

It may be of interest to point out in this connection that Cornil and associates (1933) constantly found myocardial lesions in guinea pigs infected with the typhoid bacillus. The degenerative changes ranged from loss of the cross-striations of the muscle fibers to severe cloudy swelling. Within the connective tissue a nodular or streaky exudate, essentially formed by histiocytes, was present. These lesions were typically perivascular. Edema, hyperemia and small hemorrhages were also encountered. The electrocardiogram showed disturbances of conduction.

Wells (1937) recorded an instance of acute endocarditis produced by *Salmonella paratyphi B* (*Salmonella schottmuelleri*). The myocardium microscopically showed many small foci of acute inflammation with necrosis of muscle fibers. These often were located about fibrinous emboli. The myocardium was replaced in small areas by young fibrous tissue. Meyer and Howell (1938) also observed an instance of endocarditis caused by *Salmonella paratyphi B* in which the myocardium histologically presented foci of lymphocytic infiltrations with a few polymorphonuclear leukocytes and histiocytes.

Nunes (1949) described a special type of myocarditis in typhoid fever, with presence of large mononuclear cells having basophilic cytoplasm and pale nuclei with a fine reticular pattern. These lesions were found principally in the interstitial tissue and often just beneath the endocardium or pericardium. They were most commonly present in the hearts of patients dying early in typhoid fever with intestinal lesions characterized by medullary swelling.

Kirch (1927) stated that myocarditis occurs occasionally in patients with dysentery of any variety. Knaack (1915) reported that a 20-year-old soldier had signs of myocarditis a few weeks after having suffered an attack of Hiss-Y dysentery. There was no autopsy. It may be of interest to mention here that Duvernay and Gerbay (1929) observed a patient who died suddenly,

presumably from myocarditis, after enterococcal infection.

Brucellosis. Myocarditis occurs in brucellosis more often than one would be led to expect from the literature.

Amuchastegui and Herrero (1948) described *interstitial myocarditis in 2 patients in whom electrocardiographic changes had been noted clinically.* The myocarditis appeared in the course of infection with *Brucella melitensis*. Attention was called to granulomatous lesions consisting of histiocytes, lymphocytes, plasma cells, fibroblasts, a few eosinophils and small capillaries. These granulomata were similar to those occasionally occurring in the skin.

Pyemias. Weiss and Wilkins (1937b) stated that abscesses of the myocardium are relatively rare and that the literature on this subject is meager. They remarked that, in most instances, such abscesses are metastatic manifestations of an overwhelming sepsis and that they are of more theoretic than clinical significance.

Among the necropsy reports of the Department of Pathology at the Boston City Hospital, abscesses in the myocardium were noted in 31 cases, with bacteriologic data available in 26. *Staphylococcus aureus* was responsible for sepsis in 20 cases, pneumococci in 2, *Streptococcus viridans* in 2, *Streptococcus pyogenes* in 1, and meningococci in 1. These authors give detailed autopsy findings in a 73-year-old white man. The pericardial cavity was filled with blood and the right ventricle was ruptured below the base of the pulmonary valve; over this area the myocardium was pale gray-brown and showed a few small irregular yellow points. Histologically, the ruptured area was surrounded by marked diffuse neutrophilic infiltration of the pericardium and myocardium and acute necrosis of the heart muscle. The Gram-Weigert stain showed numerous gram-positive cocci in pairs and clusters in the abscessed area. Bacteriologic examination of the blood, obtained from the cardiac cavity, yielded a pure culture of *Staphylococcus aureus*. The authors referred to reports of 7 instances of rupture of the heart by abscess in which the descriptions were sufficiently detailed to rule out other conditions.

Flaxman (1943) stated that among 14,160 autopsies, myocardial abscesses were noted in

29. This, offhand, does not seem a significant number. However, one must take into consideration that abscesses are often small and that a number of sections of the myocardium must be cut and examined to determine their presence. Thus, statistical reports on the presence or absence of abscesses in the myocardium, taken from routine autopsy records, do not give the true incidence.

It may be of interest to mention here that, among the 654 cases of spontaneous cardiac rupture collected and analyzed by Krumbhaar and Crowell (1925), abscesses were mentioned in only 3 and myocarditis in 4. Of 92 additional cases of ruptured heart analyzed by Davenport (1928), the rupture was the result of an abscess in 2. Sossai (1946) also described an instance in which rupture of the heart was caused by inflammation (abscess?) rather than infarct. Minute abscesses in the myocardium are also encountered in acute and subacute bacterial endocarditis (see page 743).

Tularemia. Myocardial changes have also been noted in tularemia. Goodpasture and House (1928) described a moderate accumulation of large mononuclear cells about the vessels of the heart. Lillie and Francis (1936), in an exhaustive study on the pathologic character of tularemia, with a review of the literature, reported on histologic studies of the heart in 14 cases. In 9 it was substantially normal, except for a variable amount of transverse fragmentation of fibers. Finely granular, cloudy, swollen and poorly cross-striated fibers were seen in 3 instances, and in 1 a diffuse interstitial round cell infiltration was described.

Experimentally, they produced tularemia in the Belgian hare. Of 28 animals with acute tularemia, focal lesions composed of nuclear debris lying among intact heart muscle fibers were seen in only 1 animal. Among 61 rabbits with late acute and subacute tularemia, focal inflammatory lesions were present in 13. In 4 of these, there were foci of lymphocytic infiltration and of interstitial caseous necrosis. In 5 others, similar necrotic foci were present, some of which, however, were surrounded by interstitial proliferations of fusiform fibroblasts or vacuolated epithelioid cells and more or less lymphocytic infiltration. One of these 14 rabbits disclosed a few granulomatous caseous foci in the wall of the left atrium. In the remaining 3 rabbits, the focal lesions were typically granulomatous in character. Two of these 3 showed a few

small perivascular nodules of epithelioid cells or fibroblasts with little necrosis and some lymphocytic infiltration. An area of dense interstitial proliferation of vacuolated epithelioid cells with atrophy and degeneration of muscle fibers was found in the ventricular wall. Also present were a few small foci of caseous necrosis and polymorphonuclear infiltration (see also page 800).

Foshay (1940) reported on his own abundant material and also reviewed the literature. He stressed the importance of previous heart disease as causing prolonged disability and death. However, cloudy swelling, loss of striations, fragmentation of muscle fibers and sparsely scattered focal cellular infiltrations between muscle bun-

dles were associated with acute instances. These lesions were seldom severe or extensive and did not occur frequently. He thought that tularemia does not seriously damage the normal heart, but that it seems likely that this severe infection causes latent coronary disease to become manifest. In a report by Stump and Quinn (1940), the myocardium of 1 patient showed a slight increase of stroma and scattered small numbers of mononuclear cells, denoting active chronic myocarditis. A second patient with tularemia had, as an incidental finding, a number of active Aschoff bodies and evidence of chronic inflammation in the myocardium.

MYOCARDIAL CHANGES IN OTHER CONDITIONS

Glomerulonephritis, Uremia, Pregnancy

As early as 1879 Goodhart implicated the heart muscle as the cause of cardiac failure in acute glomerulonephritis.

Whitehill and associates (1939) found clinical evidence of cardiac insufficiency in 71 per cent of their series of 138 patients with acute nephritis, but microscopically the heart muscle was almost always reported as being normal or, at most, slightly edematous. Darrow (1941), however, reported finding separation of heart muscle fibers, perivascular accumulations and diffuse sub-endocardial infiltrations of mononuclear cells and a few plasma cells. Gore and Saphir (1948) reported the association of myocarditis in 16 of 160 patients who died of acute or subacute glomerulonephritis. They excluded cases of acute nephritis occurring subsequent to such illnesses as scarlet fever, typhus and septicemia. The hearts were usually increased in weight and the muscle was soft and pale, with mottling or streaking. Microscopically, the inflammatory foci were small and involved only portions of a given section. The serous components of the cavities were particularly conspicuous (Figure X-49). The interstitial tissues were rendered more prominent by the presence of a faintly eosinophilic fluid and scattered inflammatory cells. Aschoff cells (Anitschkow myocytes) were often present but polymorphonuclear leukocytes were generally absent. Gore and Saphir remarked that their figure, 10 per cent of 160 cases, contrast sharply with the high incidence of clinical myocardial failure reported by others. They believed that

the discrepancy is more apparent than real because of the patchy distribution of the inflammatory changes in the heart muscle and because routine sections of the myocardium which they examined constituted but a small sample of the cardiac musculature.

Bohn and Feldmann (1947) also emphasized the relatively frequent occurrence of myocarditis in patients with acute diffuse nephritis. Myocarditis occasionally was the cause of death among German soldiers during World War II. The myocardial inflammation may not become evident until the fourth to sixth week of the nephritis.

It is well known that patients with uremia often have changes in the electrocardiogram. Lüscher (1921) found a hemorrhagic type of myocarditis associated with acute fibrinous pericarditis in a patient with typical uremia, and

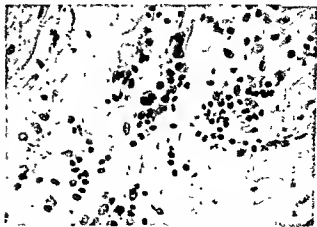


Figure X-49. Myocarditis associated with uremia. Note edema. Most of inflammatory cells are lymphocytes and a few resemble plasma cells. Hematoxylin and eosin. X 375.

termed this "uremic myocarditis." Gouley (1940) stressed the existence of a specific uremic "myocardiopathy" but rejected the term "uremic myocarditis." He found, histologically, only fatty changes of the muscle fibers with hyaline degeneration and little or no cellular infiltration. Solomon and associates (1942) were unable to demonstrate any lesions characteristic of the uremic state in the hearts of 50 patients who died in uremia. An unusual endothelial hyperplasia of the cardiac arterioles was present in 7 of 8 patients with acute necrotizing arteriolitis of the kidneys. On microscopic examination diffuse fatty degeneration with miliary myocardial necrosis was present. Acute interstitial myocarditis was found in 31 cases. Langendorf and Pirani (1947) found myocardial changes that were related to the hypertensive heart disease and, in addition, diffuse fatty degeneration, cloudy swelling of myocardial fibers and interstitial edema. While the fatty degeneration was probably caused by concomitant anemia, the cloudy swelling and interstitial edema can be ascribed to the uremic intoxication but cannot be regarded as diagnostic of uremia. They concluded that there was no evidence to support the existence of a specific so-called uremic myocarditis. The factors responsible for the changes in the electrocardiograms of patients with uremia are believed to be chronic left heart strain, myocardial changes resulting from coronary artery disease, and diffuse pericarditis, and changes in the electrolyte balance which give rise to hypocalcemia and hyperkalemia.

Most of the reports in the literature describing myocarditis in pregnancy are clinical, with electrocardiographic changes.

Thus, Walls (1947) reported myocarditis in a 34-year-old woman with a pregnancy of three months' duration. The clinical diagnosis was toxic myocarditis. Szekely and Snaith (1947) clinically studied the heart in 19 unselected cases of toxemia of pregnancy. They concluded that cardiac involvement is not uncommonly a complication of toxemia of pregnancy, some of the unusual types of heart failure occurring late in pregnancy and in the early puerperium. Some women, who suffer postpartum vascular collapse, may actually have toxemia of pregnancy with associated myocardial damage.

Gouley and associates (1937) reported death in 3 women from cardiac failure a short time following delivery. The myocardium of all 3 contained moderate numbers of lymphocytes

and macrophages, and occasional neutrophils and eosinophils. Teel and co-workers (1937) and Hull and Hafkesbrung (1937) reported similar cases with postmortem evidence of myocarditis. None of their patients had any valvular lesions.

Wallace and associates (1946) reported electrocardiographic changes in women with toxemia of pregnancy and cardiac failure. They believed that the electrocardiographic changes simulated those occasionally observed in acute nephritis. They stated that focal myocardial necrosis, edema, and cellular infiltration secondary to toxemia of pregnancy may give an electrocardiographic picture which simulates that of acute nephritis or of an atypical acute myocardial infarct. Melvin (1947) noted that "postpartal heart disease" had already been described by Virchow. He pointed out that in autopsied cases, the heart was dilated, slightly hypertrophied, and had microscopic foci of necrosis.

Fungous Infections

Since the introduction of antibiotics into clinical medicine, yeast and fungous infections of the myocardium, particularly monilliasis and aspergillosis, have increased somewhat in number. It has been said repeatedly that, following treatment with antibiotics, fungi that are ordinarily nonpathogenic may become pathogenic after disappearance of bacteria.

Blastomycosis. Kirch (1927) pointed out that rarely the heart may be involved in generalized blastomycosis. He cited the older literature but did not mention LeCount's report (1915) of a case in which about 100 miliary nodules were found in the epicardium and the histologic examination showed involvement only of the superficial parts of the myocardium.

Stober (1914) studied systemic blastomycosis and described lesions in the myocardium in his Case 6, but in the summary of his report he mentioned that myocarditis was found "in a few." Coupal (1924) found several abscesses in the left ventricle and the left atrium. The abscess contained huge organisms. The wall of the abscess was made up chiefly of small mononuclear cells and basophilic giant cells, and was diffusely infiltrated by young fibroblastic cells. Medlar (1927) reported instances of pulmonary blastomycosis, stressing the similarity of this condition

to tuberculosis. The heart on histologic examination showed a small tuberculoid structure composed entirely of mononuclear leukocytes with 3 yeast-like bodies, resembling *Torula*. Baker and Brian studied 2 instances of blastomycosis of the heart. In one patient, a firm nodule was present in the right atrium, the surface of which presented smaller elevations and ulcers. Histologically, just beneath the inner surface of the nodule, in the wall of the right atrium, were caseous areas containing blastomycetes. The second heart showed large areas of necrosis containing numerous blastomycetes and comparatively few polymorphonuclear neutrophilic leukocytes. Organisms were noted within the giant cells. Martin and Smith (1939), in a review of the literature on blastomycosis, stated that the heart was involved in 9 instances, the lesion having been found in the pericardium, myocardium and endocardium. They believed that it is possible for the cardiac lesions to develop by means of retrograde lymphatic extension.

Aspergillosis. Grekin and associates (1950) found granulomata in the myocardium and in the subendocardial regions which contained sporulating hyphae of *Aspergillus fumigatus*. We have seen 2 instances of this infection in patients who had been treated extensively with penicillin for an upper respiratory tract infection.

Actinomycosis. The rarity of cardiac actinomycosis may be inferred from the report by Sanford and Voelker (1925) who reviewed 670 cases of actinomycosis in the United States. In not a single instance was the heart involved.

Kirch (1927) also stressed the rarity of this condition, suggesting that the infection may reach the heart either as a result of hematogenous metastasis in instances of so-called generalized actinomycosis or may extend to the myocardium after a primary involvement of the neighboring structures. Primary actinomycosis of the organs of the neck also may extend to the mediastinum and thence to the myocardium.

Kasper and Pinner (1930) cited 475 instances of actinomycosis, in 5 of which there was a record of myocardial involvement. Edwards (1931), discussing actinomycosis in children, reported that the myocardium of a 10-year-old boy contained numerous minute abscesses, particularly within the right ventricular wall. The actinomycosis was primary in the bronchioles and extended secondarily into the heart (see also page 725).

Cryptococcosis (Torulosis). Crone and associ-

ates (1937) reviewed the subject of cryptococcosis. Among the organs involved in torulosis were the central nervous system and meninges, lungs, liver, spleen, adrenal glands, kidneys, testes, abdominal, thoracic and axillary lymph nodes, bone marrow and periosteum. The myocardium was not mentioned as a site of infection.

Candidiasis (Moniliasis). Polayes (1940) reported an instance of subacute endocarditis with systemic moniliasis. A cauliflower-like massive vegetation, composed of monilia, leukocytes and fibrin situated on the posterior cusp of the aortic valve, bulged into the right atrial wall, perforating at a point just above the medial leaflet of the tricuspid valve. Acute interstitial myocarditis was also present.

Histoplasmosis. Histoplasmosis (reticulo-endothelial cytomycosis) may cause myocarditis. In Crumrine and Kessel's case (1931), the heart had a gelatinous coating with several vague white nodules suggestive of tubercles over the anterior surface near the base. However, microscopically the heart showed no organism. Dodd and Tompkins (1934), reporting infection in an infant, stated that the parasites were demonstrated in all of the organs involved and in smears of the cardiac blood. Large mononuclear cells were found in practically all the tissues. The most conspicuous lesions were in the liver, lungs, spleen, lymph nodes and bone marrow. Humphrey (1940) reported 2 instances. In the first, microscopic examination of the myocardium revealed several large areas containing cells packed with organisms, numerous plasma cells and apparently immature lymphocytes. Some of these areas were so extensive as to cover a low-power field. The organisms (small coccoid dark-staining bodies with white haloes or capsules about them) were found in macrophages. In the second instance, no organisms were found in the sections of the heart. Kuzma (1947) described interstitial myocarditis with granulomatous areas in which there were macrophages containing *Histoplasma*. Menon and Rao Prasad (1945) recorded the presence of large caseous and conglomerate tuberculoid lesions situated near the junction of the septum with the pars membranacea, which had caused complete heart block; another lesion was present within the septum but situated closer to the apex.

Coccidioidomycosis. Reingold (1950) found granulomatous myocardial lesions in 3 patients with disseminated coccidioidomycosis. In 1 heart



Figure X-50. Coccidioidomycosis of myocardium. Hematoxylin and eosin X375. (Courtesy of Dr. I. M. Reingold and The Williams and Wilkins Co., Baltimore. Reprinted from *Am. J. Clin. Path.*, 20:1044, 1950.)

the organisms were found within the granulomata. (See Figure X-50.)

For a discussion of myocarditis in parasitic diseases, see Chapter XI.

Rheumatoid Arthritis

Myocarditis in rheumatic fever has been discussed in Chapter IX. Mention must be made here, however, of myocardial changes encountered in so-called rheumatoid arthritis. Unusual cardiac lesions associated with this disease were described by Baggenstoss and Rosenberg (1944). Focal collections of lymphocytes, plasma cells and reticular cells were scattered throughout the interventricular septum. In 2 instances, evidence of healed rheumatic myocarditis was inferred from the presence of perivascular "onion-skin" scars. However, more characteristic changes were found in the endocardium. The predominating structural unit of this inflammatory process was roughly spherical. The central zone consisted of an acidophilic, apparently necrotic tissue in which, however, a

distinct reticular or collagenous framework was still recognizable. Adjacent to the necrotic center was a zone of large, elongated, radially directed cells with large pale-staining nuclei and faintly basophilic cytoplasm. Many cells were multinucleated. The most striking features of these cells were their large size and their radial or palisade arrangement. Peripheral to the intermediate zone of palisaded cells was a broad and imperfectly demarcated zone of inflammatory reaction. These nodules are most often found in the endocardium, but occasionally extend into the myocardium. (See also page 686.)

In a report by Gruenwald (1948), the endocardium and muscular wall of the right atrium had been completely replaced in some areas by this granulation tissue. Mallory's stain for collagenous fibers and Gomori's method of silver impregnation revealed large numbers of fibers in all layers of the granuloma.

In a study of 16 patients with rheumatoid arthritis, Sinclair and Cruickshank (1956) found widespread systemic involvement. Granulomata of the heart were encountered 5 times, rheumatoid

endocarditis was seen in 8 patients, and some combination of myocarditis, coronary arteritis or pericarditis was present in 5 patients all of whom showed clinical features of cardiac involvement. The lesions in the myocardium were characterized by both *granulomatous* and *nonspecific* types of inflammation. The authors suggested that if tissues other than the joints are involved, the condition should rather be termed "rheumatoid disease." They did not regard the changes encountered to be characteristic of a collagen disease.

While not related to rheumatoid arthritis, the occurrence of myocardial changes in Libman-Sacks endocarditis, lupus erythematosus, dermatomyositis, and scleroderma may be discussed here. For a fuller discussion of changes in the myocardium in Libman-Sacks endocarditis, see Chapter on Endocarditis.

Libman-Sacks Disease and Lupus Erythematosus *Dermatomyositis and Scleroderma*

Libman-Sacks Disease. Libman and Sacks (1923), in their description of a special type of valvular and mural endocarditis, found that microscopically, the endocarditic process had invaded the adjacent myocardium rather deeply, with destruction and replacement of many muscle fibers, foci of round cell infiltration and extreme fibrosis.

Gross (1940) principally found vascular alterations in the blood vessels of the myocardium. Granular plugs were often seen in the lumina of the myocardial arterioles and venules (platelet thrombi). Also present were foci of interstitial inflammation consisting of polymorphonuclear leukocytes, lymphocytes, macrophages and plasma cells. He also described changes in *lupus erythematosus* in which the principal cells in the myocardium were plasma cells and peculiar large mononuclear cells, in addition to numerous histiocytes and fibroblasts. Klemperer and associates (1941) stated that in *lupus erythematosus* alterations of the collagen are often encountered in the myocardium. The fibers appear swollen and stain deeply with eosin, and usually infiltrations of lymphocytes are found. Fibrinoid degeneration and necrosis of the walls of small arteries are also encountered, but myocarditis is not common.

Humphreys (1948) found focal myocarditis in most of the 21 cases of *lupus erythematosus*

which she reported. In the mildest cases, the lesions were indistinguishable from minor scarring of rheumatic or atherosclerotic disease, or were indeterminate small exudative lesions of doubtful significance. Obviously, these may have been unrelated to the main disease. More significant were the fine scars, like those of small infarcts, the increased density of collagen along many or most of the intermuscular septa, and the thickened small arteries. Fresh fibrinoid necrosis of collagen or of vessel walls was easily demonstrable in the more severe cases. In a considerable number of hearts, there was marked loosening of the fibrous substance and fatty degeneration of myocardial fibers. No active rheumatic lesions were seen.

Dermatomyositis. Kinney and Maher (1940) made an extensive study of 2 patients with dermatomyositis (Figure X-51). In 1 of their patients, the muscle fibers of the left ventricle were separated by edema. An area of more severe edema, with interstitial infiltration of lymphocytes, imperceptibly merged with the relatively uninvolved myocardium. Throughout this area were patches of muscle



Figure X-51. Myocarditis associated with chronic dermatomyositis. X 140. (WCGit, 53 P 369.)



Figure X-52. Myocarditis in subacute bacterial endocarditis. Note perivascular infiltration of lymphocytes. Hematoxylin and eosin. X 200.

fibers which were poorly stained and showed loss of cross-striation. Large numbers of small lymphocytes, together with a few monocytes, were present between the muscle fibers and surrounding the blood vessels. Within the myocardium of the right ventricle were found occasional polymorphonuclear leukocytes, together with fibroblasts, proliferating capillaries and muscular debris. In their second case, they found, in the myocardium of the left ventricle, infiltrations of lymphocytes with minimal degeneration of muscle fibers, accompanied by an increase of fibrous connective tissue.

Scleroderma. In this connection, it may be appropriate to mention myocardial changes that occur in cases of scleroderma, principally because of the relationship between dermatomyositis and diffuse scleroderma, as discussed by Brock (1934). Weiss and associates (1943) reported in detail the postmortem findings in 2 patients with generalized scleroderma. These patients were part of a group of 9, all of whom had signs and symptoms of heart disease. The authors concluded that both the clinical and pathologic studies indicated that the sclerodermatous process is not confined to the skin but involves all organs. The cardiac failure is caused by myocardial scarring. The scars were unusually vascular and it was thought that they bore more resemblance to granulation tissue than to scars resulting from atherosclerosis or old myocardial infarction. No infarcts or deposits of hemosiderin were encountered. One of the hearts contained

many fibroblasts but only an occasional lymphocyte and mononuclear cell in a few foci.

East and Oram (1947) also reported a case of scleroderma. Scattered throughout the myocardium were numerous areas of fibrosis. The patient had complete heart block and died from heart failure. They believed that, for some unknown reason, the cardiac muscle fibers disappeared in patches and were replaced by new connective tissue. They remarked that their concept of the disease "might be summarized by the title of one of Strauss' tone poems, *Death and Transfiguration*."

Myocarditis in acute bacterial endocarditis and subacute bacterial endocarditis (Figure X-52) has been discussed in connection with the endocardial lesions.

Isolated Myocarditis. Allergic Myocarditis

Isolated myocarditis is one of the most interesting types of myocarditis. It is of unknown origin, not accompanied by endocarditis or pericarditis, and occurs in patients who have no primary disease that may be correlated with the myocarditis. It may be present in an apparently healthy person who, more or less suddenly, develops progressive myocardial weakness and succumbs quickly.

Clinically, the outstanding manifestations are progressive myocardial failure with a weak rapid pulse, low arterial pressure, and an increase in the area of cardiac dullness. Electrocardiographic changes are often encountered but usually misinterpreted. Precordial pain may be present. The disease may occur at any age, although young people seem more frequently affected. Therefore, atherosclerotic heart disease can usually be ruled out. There is no history of rheumatic fever. The patients often die unexpectedly, as did 10 of 13 patients reported by Saphir (1942b).

Nomenclature. Earlier writers have used the terms "Fiedler's myocarditis," "interstitial," "circumscribed," "diffuse," "isolated," "idiopathic," "pernicious" and "granulomatous," singly or in combination, to describe the disease. Although Fiedler (1899) termed this myocarditis "acute interstitial," it is clear from Fiedler's report that Schmorl, who studied the hearts of Fiedler's cases microscopically, described parenchymatous changes also in some of these with outspoken necrosis. The

2 cases reported by Ware and Chapman (1947), termed "chronic fibroblastic myocarditis," may also be classified as isolated myocarditis since they resemble those described by Boikan (1931) as pernicious myocarditis. However, these authors stated that it is possible that the etiology of this myocarditis may be traced to some acute or chronic infectious disease. Scott and Saphir (1929), who were the first to report cases in the American literature, referred to "isolated myocarditis."

The literature on this subject has been reviewed previously. Among relevant reports may be mentioned those of Covey (1942); Didion (1943); Hertzog and Hayford (1947); Marcuse (1947); House (1948); Tedeschi and Stevenson (1951), and Williams and associates (1953). Isolated myocarditis has often been reported in children (Bluhdorn, 1924; Kenny and Sanes, 1933; Maslow and Lederer, 1933; Lindberg, 1938; Smith and Stephens, 1938; Greenebaum *et al.*, 1941; Conlin and Mantz, 1953; and others). Saphir and co-workers (1944) referred to 41 such instances. Myocarditis was present in 8 children who were among the 36 patients of Marcuse's series, and House recorded its occurrence in 4 children. Jones and Marshall (1946) and Raeburn (1948) found this type of myocarditis in an 11-month-old infant, and Drennan (1953), in newborn infants.

Pathologic Features. Grossly, the hearts are usually enlarged and dilated. Kiss (1947) emphasized the occurrence of hypertrophy in hearts having myocarditis. The myocardium is pale gray, often tinged faintly yellow with fine gray or red streaks. Histologically, the lesions are either diffuse or circumscribed and principally interstitial in location, although rarely the heart muscle fibers may be involved. In general, no characteristic cellular accumulations are present, nor does one particular type of cell predominate (Figure X-53).

Only Marcuse stated that he constantly found in his cases elongated cells with distorted nuclei, morphologically not identical with Aschoff cells or Anitschkow myocytes. Usually lymphocytes and endothelial leukocytes are the most commonly encountered cells (Figures X-54 and 55). Polymorphonuclear and eosinophilic leukocytes, however, are also present, and Saphir thought

that mast cells, which are normally found within the interstitial tissue of the myocardium, seemed more numerous than normal. Transitions from the inflammatory cellular exudate to scar tissue are often found. House's first case disclosed widespread and diffuse loss of cardiac musculature with moderate infiltration of polymorphonuclear leukocytes, lymphocytes, plasma cells, macrophages and large mononuclear cells. The majority of the muscle fibers had been replaced by young granulomatous tissue. He suggested coronary occlusion as a possible factor, even though a careful examination did not reveal any such lesion. Because of the age of the patient (21 days), House also considered an infectious process developing *in utero*.

Isolated myocarditis has also been reported in infants and children (see Tedeschi and Stevenson, 1951; Williams *et al.*, 1952; and Drennan, 1953). Apparently in recent years, the number of such reports has increased. We also have seen an increase in the number of cases of isolated myocarditis in children. However, some of the reports probably represent viral myocarditis, even though the causative virus was not demonstrated.

Granulomatous Myocarditis. In other instances of isolated myocarditis, granulomas with giant cells are encountered (Figure X-49). Neither tubercle bacilli nor spirochetes can be demonstrated in these hearts, although a history of tuberculosis or syphilis may be obtained (Taussig and Oppenheimer, 1936). In such instances, there usually are smaller or larger areas of necrosis at the periphery of which many lymphocytes, eosinophilic leukocytes and a few endothelial leuko-

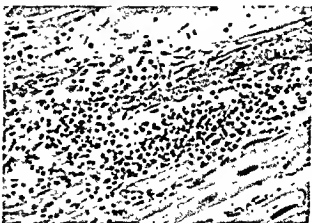


Figure X-53. Isolated myocarditis. Note that inflammatory cells are mainly lymphocytes and only a few are "cardiac histiocytes." Hematoxylin and eosin. X 325.

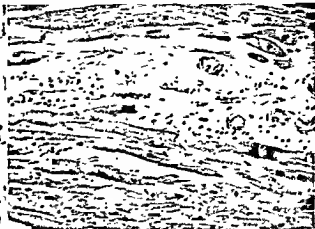
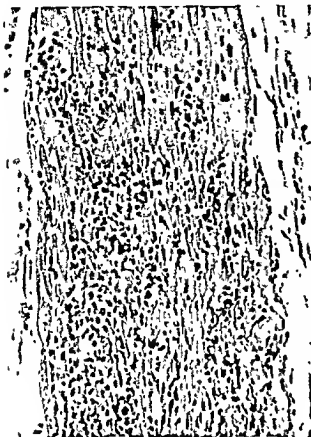


Figure X-54 (left). Subacute isolated myocarditis. X 240. (WCGH, 58 P 369A.)

Figure X-55 (right upper). Isolated myocarditis. Note loss of myocardial fibers, few fibroblasts, and inflammatory cells. X 140. (WCGH, 58 P 369B.)

cytes are present, but there is no particular predominance of any of these types of cells. Likewise, the necrosis may be insignificant. The number of giant cells is conspicuous and their nuclei are arranged more or less toward the periphery. Some of these giant cells resemble those seen in tuberculosis, while many others are typical muscle giant cells. Numerous circumscribed areas contain no necrosis but consist of lymphocytes, eosinophilic leukocytes, and a few giant cells (Figure X-56). These regions are richly vascularized, with thin-walled vessels. The adjacent myocardium discloses a diffuse infiltration, predominantly of eosinophilic leukocytes and lymphocytes. Again, neither spirochetes nor tubercle bacilli are demonstrable. Because the lesions often contain many giant cells but no outspoken granulomas, the term "giant cell myocarditis" may be preferred to "granulomatous myocarditis."

Earlier reports of this type of myocarditis were made by Saltykov (1905); Baumgartner (1915); and von Gierke (1921); and relevant reports have been given by Miller (1933); Sidi

(1936) who reviewed the literature; Magner (1939); Hansmann and Schenken (1938); Jonas (1939); Saphur (1942b); Kean and Hoelenga (1952), and Goldberg (1955).

Other Conditions. In discussing Miller's case, Lillie (1934) remarked that in experimental *tularemia* a granulomatous myocarditis is not infrequently found. This is interesting because the question immediately arises whether there may be other infectious diseases that also produce granulomatous lesions, in which the causative organism cannot be demonstrated. Blastomycosis can be ruled out because blastomycetes are recognizable in sections. Sidorov (1935) reported a case of granulomatous myocarditis caused by *Balan-tidium coli* and demonstrated the organism.

Trichinous myocarditis usually does not have a characteristic histologic picture, although occasionally a stray young larva may be found in the myocardium (see Figures XI-5 and 6). *Trichina* larvae, however, never encyst in the myocardium (Gould; see page 831). Histologically, the myocardium (Figure X-57) shows focal or diffuse infiltrations

of neutrophilic leukocytes, lymphocytes, and a few mononuclear leukocytes and plasma cells. Usually many eosinophilic leukocytes are also present, although their absence is occasionally stressed. In isolated (Fiedler's) myocarditis, also, a predominance of eosinophils may be rarely noted (Magner, 1939). The muscle fibers are degenerated or actually necrotic. The absence of the larvae, as stated above, does not preclude a diagnosis of trichinous myocarditis.

In a personal observation, small granulomatous lesions were found in the myocardium in a case in which *Trichinella spiralis* was encountered in the diaphragm. Histologically, the changes in the myocardium resembled those which are seen in granulomatous myocarditis and in diffuse isolated myocarditis. Only the discovery of trichinae in the diaphragm prevented us from classifying this as isolated myocarditis. Weller and Shaw (1932) also noted the similarity of these two conditions, but Libman questioned the similarity of "eosinophilic" and isolated myocarditis, as reported by Smith and Stephens (1938). Thus, it seems clear that if attention is focused on the heart only, not only trichinous myocarditis, but

perhaps also other types, may well be confused with isolated myocarditis. On the other hand, the question must be raised if in some instances isolated, particularly granulomatous, myocarditis may not result from one of the known causes of inflammation.

Myocarditis may be found in association with toxoplasmosis (Figure X-58A and B). Since the parasites are usually not recognized in the sections, this form of myocarditis may be confused with isolated myocarditis. Paulley and associates (1956) discussed focal myocarditis caused by *Toxoplasma*. They found that myocarditis may be the only sequela of an earlier infection. The myocarditis shows no characteristic features, but only excessive interstitial fibrosis. In their cases the serologic test and the complement-fixation test for *Toxoplasma* were positive. (See also page 829 and Figure XI-3.)

Myocarditis in *Chagas' disease*, in the absence of organisms, may be confused with isolated myocarditis. Laranja and associates (1956) studied the clinical, epidemiologic and pathologic aspects of *Chagas' disease* and presented the autopsy findings in 21 cases. The outstanding changes were dilatation and hypertrophy of the heart, particularly of the right atrium and ventricle, focal endocardial fibrosis, mural thrombosis, dissemi-

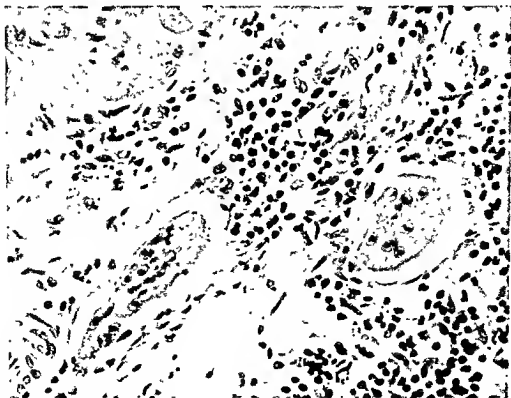


Figure X-50. Giant cell granulomatous myocarditis. X-435. (Courtesy of Armed Forces Institute of Pathology, Acc. 65,448.)

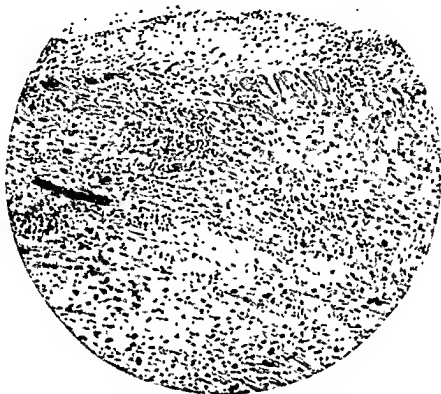


Figure X-57. Trichinous myocarditis. X175. (From Gould, S. E.: *Trichinosis*, Thomas, 1945.)

ated inflammatory changes of the myocardium (with presence of lymphocytes, plasma cells, macrophages, eosinophils and polymorphonuclear leukocytes), and degeneration and fibrosis of the myocardium. A granulomatous form of myocarditis was found in 5 cases. Leishmanial forms of *Schizotrypanum cruzi* were present in all cases, sometimes in macrophages. They were found with ease in 3 cases and with difficulty in the remainder. Venous hyperemia and obliterative changes of the small and medium-sized branches of coronary arteries were seen in some cases. These changes, together with the focal endocardial fibrosis obviously blocking thebesian veins, were held responsible for myocardial ischemia and the consequent fibrosis.

It might be of interest to mention that a chronic type of myocarditis, which probably falls into the classification of isolated myocarditis, was described in a young camel that died unexpectedly (Stunzi, 1947). The lesion consisted of scars with necrosis, many giant muscle cells, and foci of calcification.

Lindberg's report of isolated myocarditis is noteworthy because of his suggestion that the

initial changes may be of *serous inflammation*, similar to those found by Wenckebach (1934) in the beriberi heart, and described by Rossle (1934), and Eppinger and associates (1935). It is thought that the serous exudate of this type of myocarditis stimulates growth of connective tissue, and that marked fibrosis ensues.

The myocarditis described by Boikan (1931) and by Lindberg (1938) may perhaps have shown a "serous" component in its initial stage. Smith and Furth (1943) remarked on the relation of isolated myocarditis to the beriberi heart. Eppinger and associates also mentioned burns as possible causes of serous inflammation. Cases of isolated myocarditis are likewise reported in which burns are suggested as the possible etiologic agent (Zuppinger, 1901; Kaufmann, 1922).

A number of attempts have been made to identify isolated myocarditis as a type produced by chemicals, such as sulfa drugs, and also as the result of *hypersensitivity*. Franz (1937) described myocardial lesions which he thought may have been the result of the administration of *epinephrine*, or were possibly caused by hypersensitivity to epinephrine. Šikl, as early as 1936, asked if

isolated myocarditis might not be classified as "idiosyncratic-allergic," rather than as "idiopathic" in the sense of unknown origin. He described 2 instances of myocarditis which followed administration of *neosalvarsan* to patients with syphilis. Both showed an acute eosinophilic myocarditis with granulomatous lesions, neither tubercle bacilli nor spirochetes could be demonstrated. In reviewing the literature of so-called idiopathic myocarditis, he believed that there might be a few instances which were the result of hypersensitivity, particularly those having a history of urticaria or exanthematous skin lesion. French and Weller (1942) described interstitial myocarditis, with many eosinophilic cells, in the hearts of 126 patients whose sole common factor was that one or more *sulfonamide* drugs had been administered shortly before death. Wells and Sax (1945) reported an instance of diffuse isolated myocarditis in which sulfadiazine was regarded as the etiologic agent. Microscopically, neutrophils predominated, and there were occasional eosinophils and monocytic phagocytes and rare lymphocytes. French (1946) described histo-

pathologic lesions in the myocardium as the result of hypersensitivity to sulfonamide chemotherapy. The characteristic cell was the acidophilic histiocyte, also found were variable numbers of other mononuclear and polymorphonuclear cells, both acidophilic and neutrophilic. These were either perivascular in distribution or diffusely distributed between the cardiac muscle fibers. Necrosis was neither constant nor prominent, but did occur in the more severe cases. Cellular infiltrates were present throughout the walls of capillaries and venules. Simon (1943) summarized the pathologic lesions that follow administration of sulfonamide drugs.

Rich (1942) described a case of recent periarthritis nodosa with diffuse inflammatory cell infiltration of the myocardium, composed of mononuclear and polymorphonuclear cells, including eosinophils. Tissue from the scrotum, removed 18 days before death and prior to administration of a sulfonamide, was examined on biopsy. There had been no evidence of acute periarthritis within the scrotum at that time, but at autopsy numerous vascular lesions were found in the tissue im-

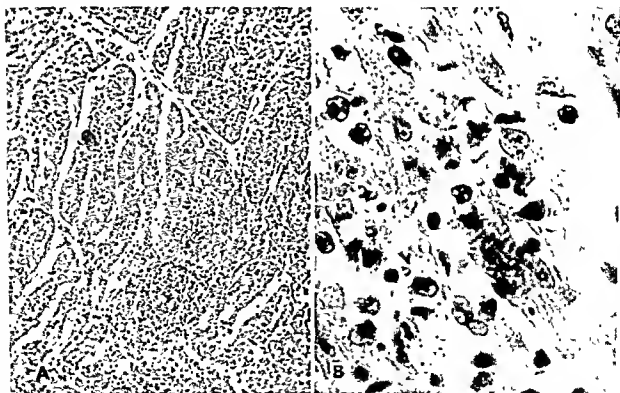


Figure N-58A (left). Toxoplasmosis. Note, in upper left quadrant of figure, a pseudocyst in cross section, with almost no surrounding inflammatory reaction. A high magnification of this pseudocyst is shown in Figure N1-3 on page 829. The right half of the figure shows scattered and focal myocarditis. X 150. (WCGH, 58 P 360.)

Figure N-58B (right). Inflammatory reaction in myocardium adjacent to section of pseudocyst of *Toxoplasma gondii*. X 1050. (Courtesy of Dr. Clyde Swartzwelder.)

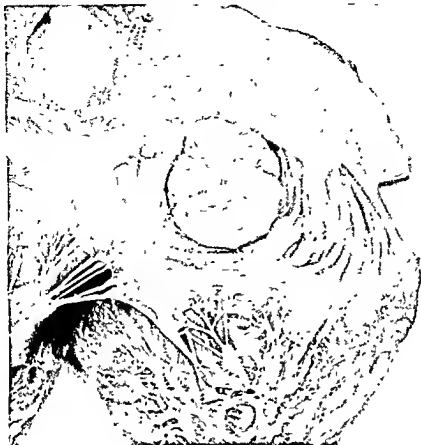


Figure X-59. Tuberculoma of myocardium projecting into endocardium. (Courtesy of Peder Lund, Medical Illustration Laboratory, Veterans Hospital, Hines, Illinois.)

mediately adjacent to the region of the scrotum from which tissue had been taken for biopsy. Because the periarteritis was obviously the result of the hypersensitivity to a sulfonamide, the myocarditis was also thus interpreted. On the other hand, Merkel and Crawford (1942) found no evidence of myocarditis in 5 patients whose death was attributed to sulfonamide drugs.

The relationship of hypersensitivity and rheumatic carditis is discussed elsewhere. It might be mentioned in this connection that Rich and Gregory (1943b) and a number of other investigators described in their experimental animals various myocardial lesions which were highly suggestive of specific lesions seen in the myocardium of patients with rheumatic fever. They emphasized that these lesions are the result of hypersensitive reactions of the anaphylactic type. While it is true that some of these myocardial lesions do resemble Aschoff bodies, myocardial changes described in isolated myocarditis in no way resemble those seen in rheumatic myocarditis.

Furthermore, acute panarteritis, which also occurs as one manifestation of the anaphylactic type of hypersensitivity (Rich, 1942a; Rich and Gregory, 1943a), is not a feature of isolated myocarditis.

Waugh (1952) described myocarditis, combined with arteritis and granulomata in various organs, which apparently resulted from sensitivity to penicillin. von Albertini and Grunbach (1938) found experimentally that virulent organisms introduced into a partially immunized animal produced the same type of lesions as were produced in the normal control animal with similar organisms of less virulence. For that reason they thought that allergy was not significant in the etiology of endocarditis or myocarditis.

In an experimental study, Gray (1949) found cardiac lesions resembling those seen in rheumatic hearts and also those encountered in experimental anaphylactic hypersensitivity, in a high percentage of control Swiss mice. Treatment with multiple parenteral injections of egg white failed to influence the incidence and the severity of these lesions. Because of the recent interest in experi-

mental myocardial lesions resembling myocarditis seen in rheumatic fever, it was emphasized that such lesions may be found in normal mice.

Jaffé (1946, 1955) has repeatedly stated that chronic myocarditis in the sense of isolated or Fiedler's myocarditis is exceedingly frequently encountered in Venezuela. However, he believes that this myocarditis is the result of an allergic reaction against *necrotic myocardial fibers*. Because the reaction of the *interstitial tissues against the muscle necrosis* is always the same, even though various agents might have caused the original necrosis of the myocardial fibers, such types of myocarditis are morphologically identical. Thus, Jaffé stated that isolated myocarditis may be caused by syphilis, bilharziasis, necator infestations and also beriberi and Chagas' disease. The original disease which had caused the myocardial necrosis may no longer be demonstrable but the myocardial lesions may remain (Jaffé).

Marcuse (1947) mentioned the following as possible causes of isolated myocarditis: bacterial infection, virus infection, sensitization to various substances, drugs causing increased heart action, dietary deficiency including general malnutrition, potassium deficiency (see page 522), combined deficiency of potassium and vitamin B. *Viral infection* as a cause of isolated myocarditis has been suggested a number of times. (See Covey, 1942; Finland *et al.*, 1945; Schmidt, 1948.)

In an extensive study, Stoeber (1952) pointed out that Fiedler's myocarditis is principally interstitial in nature, while changes in the myocardial fibers themselves, especially necrosis of myofibers, are more characteristic of viral myocarditis. We also have repeatedly observed necrosis of isolated muscle fibers in viral myocarditis. On the other hand, in the granulomatous variety of isolated myocarditis, necrosis of myofibers is common. However, in viral myocarditis, granulomata do not occur. Reports of isolated myocarditis in more than one member of the same family (Blanshard (1953) suggest the presence of a transmissible agent. Such cases may be viral myocarditis misdiagnosed as isolated myocarditis, again pointing to the difficulties encountered in the differential diagnosis between these two types of myocarditis.

In summary, isolated myocarditis is a type of myocarditis of unknown origin which is not accompanied by endocarditis or pericarditis.

It occurs in patients who have no other disease that may be correlated with the myocarditis. This myocarditis may also be present in apparently healthy persons who, more or less suddenly, develop progressive myocardial weakness and quickly succumb. Anatomically, isolated myocarditis does not vary in histologic detail from the lesion that is occasionally encountered in the course of acute infectious diseases. A diffuse and a granulomatous type can be distinguished. The latter is much rarer, and morphologically resembles somewhat the granulomata of tuberculosis and syphilis. Histologically, muscle giant cells are often recognized. Although nothing is known as to the cause of either the diffuse or granulomatous form, it is imperative in every instance to examine histologically other organs and structures besides the heart, in search of the causative agent, as in trichinosis and tularemia. Hypersensitivity to various chemical compounds, certain vitamin deficiencies, allergic reaction to either necrotic muscle fibers or some other agent, or a virus infection, have been regarded as responsible. However, it would seem wiser to classify myocarditis of unknown origin, not as isolated myocarditis, but as "hyperergic" or "chemical," as the case may be. With increasing knowledge, the diagnosis of "isolated myocarditis" will become less frequent.

Tuberculosis

Horn and Saphir in 1935 reviewed the literature on involvement of the myocardium in tuberculosis. Three main types can be distinguished, namely, the nodular (Figure X-59), the miliary, and the diffuse infiltrative types. The latter should be accepted only if the histologic changes are undoubtedly characteristic of tuberculosis, or if the tubercle bacillus can be demonstrated either by guinea-pig inoculation, culture, or staining methods. Otherwise, this form of tuberculosis cannot be distinguished from the so-called specific productive myocarditis (Saltykow, 1914). For similar reasons, it is difficult to attribute to a tuberculous origin, fibrous myocardial lesions which may be present in the heart of a person dying of tuberculosis.

Hence, the term "chronic interstitial tuberculous myocarditis" should be discarded.

Horn and Saphir (1935) reported military tuberculosis of the myocardium in 3 children, 1 of whom also had a conglomerate tubercle of the heart. The literature discloses that most instances of military tubercles in the myocardium occur in children. This may indicate that it is easier to find military tubercles in the hearts of young persons dying of military tuberculosis because of the relatively larger areas examined histologically.

Among 97 children with myocarditis studied by Saphir and associates (1944), myocarditis was associated with tuberculosis 4 times. Actual tubercles were found in 2 infants. Both had diffuse military tuberculosis and 1 of them had tuberculous leptomenigitis. In 2 other children, 2 months and 6 years old, respectively, who also had diffuse military tuberculosis, the inflammation in the myocardium was diffuse and nonspecific. These lesions were predominantly perivascular. Tubercle bacilli could not be demonstrated in these hearts and the myocarditis cannot be classified as "tuberculous." The clinical findings in these 2 infants did not differ appreciably from those of the 2 previously mentioned children who had tubercles in the myocardium, or from those of children who had the same type of generalized tuberculosis but no myocardial involvement.

Nonspecific inflammatory cells observed in the myocardium of tuberculous patients may resemble those seen in Aschoff bodies (Masugi *et al.* 1937). Roberts and Lisa (1943) discussed the relationship of these nonspecific inflammatory lesions to the lesions seen in rheumatic fever. It must be realized, first, that it is always possible to encounter tubercles and Aschoff bodies in the same heart and, second, that simply because a lesion resembles an Aschoff body morphologically is no proof that the lesion in question signifies rheumatic fever. Apparently because of this resemblance and because of the finding of tubercles and Aschoff bodies in the same heart, Masugi and his associates suggested that rheumatic fever might be of tuberculous origin.

Amersbach and associates (1931) reported the presence of tubercle bacilli in tonsillar tissues in patients with recurrent rheumatic arthritis. It seems probable that these authors were dealing with patients who had both diseases.

It has also been suggested that morphologically nonspecific inflammation in the myocardium in tuberculosis may be the result of a secondary non-tuberculous infection. This seems more logical

because one occasionally finds myocarditis associated with other pulmonary lesions, such as bronchopneumonia and bronchiectasis.

An unusual myocardial involvement was described by Jones and Tilden (1942) in an 11-year-old girl with tuberculous cervical lymphadenitis, who died unexpectedly. The autopsy disclosed conglomerate tubercles in the myocardium, which had caused a tuberculous (mycotic) aneurysm at the base of the left ventricle. Death resulted from rupture of the aneurysm and consequent hemopericardium. Tuberculous myocarditis with endocardial thrombosis and subsequent embolism from these thrombi has also been reported by Beebe and Coleman (1915). The nodular variety of tuberculosis (tuberculoma) is the most frequent form (Figure X-59). Rauchwerger and Rogers (1947), who reported such an instance, stated that this form usually occurs as yellow-gray, rounded, fairly firm nodules which may vary in size from less than a centimeter to that of an egg. They may be well defined or may merge with the surrounding parenchyma. The common site is the wall of the right atrium. Their ability to produce symptoms, of course, depends upon their size and location. With a few notable exceptions, most of the reported cases have been without subjective or objective signs of cardiac involvement. Rosenbaum and Linn (1948) also found, in the reported cases, that the wall of the right atrium is the most common site of nodular tuberculosis. They reported an instance of tuberculoma of the interatrial septum of the heart.

In a patient with paroxysmal ventricular tachycardia Schnitzer (1947) found, at autopsy, military tuberculosis of the myocardium involving the interventricular septum.

Sarcoidosis

The myocardium may be involved in sarcoidosis. Saphir (1942a) has referred to the older literature. Johnson and Jason (1944) thought that perhaps some of the cases reported as "granulomatous myocarditis" (isolated myocarditis; see above) might have been examples of sarcoidosis of the myocardium.

Scotti and McKeown (1948) referred to 12 such instances reported in the literature, and reported a case of their own. The epicardium or pericardium was involved 3 times, the myocardium alone 3 times and the pericardium and myocardium 7 times. Three of these 13 patients died

unexpectedly. Grossly, the myocardium was dark brown and firm and showed no abnormalities. Microscopically, nodules composed of epithelioid cells, lymphocytes, and occasional giant cells were found in the subepicardial fat. One of these nodules was adjacent to a coronary artery but did not involve its wall. Multiple granulomas were present in sections of the myocardium of the left atrium, in the interventricular septum, and in the papillary muscles and the wall of the left ventricle. In some cases, small collections of lymphocytes without other cellular components were also seen in the myocardium. Granulomatous lesions were also noted in lymph nodes, lungs, liver and the prostate gland. Unexpected death was attributed to the active lesions and to prominent fibrosis extensively involving the myocardium. Rucker and Clark (1949), in a review of sarcoidosis, found the heart involved only twice among 195 cases. Stephen (1954) reported sudden death of a patient with sarcoidosis which involved the myocardium. Peacock and associates (1957) reviewed 28 cases of sarcoidosis in which typical granulomatous lesions were seen in the myocardium, and added a case of their own. They emphasized that sarcoid nodules may be associated with heart block and may be responsible for unexpected death.

Syphilis

It is still controversial whether syphilis may involve the myocardium in the form of a non-specific subacute or chronic inflammation. Excluding congenital syphilis of the heart, gummas in the myocardium or gummatous myocarditis (microscopic gummas), the controversy centers about the possible occurrence of a diffuse myocarditis that may be brought about by the presence of the *Treponema pallidum*.

In 1932 Saphir reviewed the literature pertaining to so-called "chronic syphilitic myocarditis" and listed the characteristics of syphilitic myocarditis as recorded in the literature. A critical consideration revealed that, morphologically, this diagnosis could not be made in any of the reviewed cases in the absence of gummas. He summarized the findings in 130 hearts which had associated syphilitic aortitis and insufficiency of the aortic valve. The myocardium in these hearts showed no morphologic changes which could be interpreted as syphilitic. All the changes observed

might be encountered in other conditions. In this study the findings of Warthin, who believed that syphilitic myocarditis is a frequent finding, were analyzed. Attempts were made to duplicate Warthin's (1918) demonstration of spirochetes. (For references to Warthin's extensive studies, see Saphir, 1932.) Using the autopsy material at the Michael Reese Hospital and employing first Warthin's staining method and later a special technique devised in the laboratory of this hospital (Garvin, 1938), a diligent search proved futile, in none of these hearts were spirochetes found. Gore (1947) remarked that Warthin's assertion that myocarditis is frequent in this disease has acquired a tenacious hold, with the result that physicians are prone to make a diagnosis of syphilitic myocarditis. He concluded that there is an abundance of irrefutable evidence that, except for a rare gumma, myocardial changes in cardiovascular syphilis can be attributed almost entirely to vascular changes: narrowing of the coronary ostia or atherosclerosis. Gore (1947) confirmed these observations in a review of material available at the Armed Forces Institute of Pathology.

As far as the patient with syphilitic heart disease is concerned, it cannot be overemphasized that in every case, sooner or later, the heart will be fatally damaged (Norris, 1937). From the point of view of the clinician, it does not make much difference whether the myocardial damage is the result of primary changes at the mouths of the coronary arteries resulting from syphilitic aortitis, or is caused by primary inflammatory changes in the myocardium itself. However, it seems clear, from numerous reports and from clinical observations in general, that when the blood supply of the heart is restricted, particularly if the interference is at the orifices of the coronary arteries, the resulting condition is more serious than that which is caused by an inflammatory process in various foci in the heart muscle other than the conduction system. For this reason, the older clinicians aptly said that the first failure of a syphilitic heart is usually the last.

Saphir (1932) has pointed out that infiltration by round cells, even in a perivascular location, and occurrence of scarred areas in various types of myocarditis are not of themselves pathognomonic of syphilis. Myocardial inflammatory changes may occur in syphilitic patients, but the changes are not necessarily syphilitic in origin.

Šikl (1936) stated that, in a patient showing symptoms of myocarditis and having a positive

Wassermann reaction, myocarditis may or may not be syphilitic, since it may represent a mere coincidence of some nonspecific process in a patient with venereal infection. Even the apparent effectiveness of antisyphilitic therapy may be misleading.

Reifenstein (1936) reported an instance of acute myocarditis simulating acute myocardial infarction. He pointed out that pathologists have been unable to distinguish the fibrous changes found in the myocardium in known syphilis from the fibrous changes found in other conditions, including atherosclerosis. This deficiency, as well as the failure to find spirochetes in the myocardium, has been used as evidence against Warthin's concept that a specific form of myocarditis is found in syphilis. Reifenstein felt that it was unfortunate that the discussion on syphilis of the myocardium had centered around the question of occurrence of a specific form of myocarditis other than the gummatous type. He stated that there is no question that gummata may occur in the myocardium just as in other organs or structures. The occurrence of gummatous myocarditis is accepted generally, the only question is whether there is an acquired diffuse syphilitic type of myocarditis in the absence of demonstrable spirochetes in the myocardium.

From the foregoing, it is clear that a number of changes are found in the myocardium in syphilitic aortitis, particularly in those also showing aortic insufficiency and narrowing of the mouths of the coronary arteries. It is also clear that a number of patients who have syphilitic heart disease (syphilitic aortic insufficiency or coronary arteritis) have acute infectious diseases which *per se* may cause a nonspecific type of myocarditis.

Clawson (1941) examined microscopically 5 blocks from each of 105 hearts with syphilitic aortitis. A few small fibrotic areas of the type commonly seen in hearts with coronary sclerosis were encountered. Also small proliferative inflammatory areas were noted in a few hearts and an occasional patch of lymphocytic infiltration was present in a relatively small number, but syphilitic myocarditis was not mentioned. Blocks from 71 hearts were stained by the Levaditi method and examined for spirochetes, but none were found.

Norris (1939) found gray or pale white, fairly well-defined spots within the wall of the left ventricle, surrounded by zones of hyperemia which he regarded as characteristic of syphilitic myocarditis. Histologically he encountered infiltrations of lymphocytic cells, fibroblasts with an

occasional giant cell and many plasma cells. There also were many new thin-walled blood vessels, a number of which were surrounded by lymphocytes.

Mention must also be made of the so-called "critical" (malignant) syphilitic myocarditis of Warthin (1925). Corrigan (1941) studied this subject and reviewed the pertinent literature. She reported myocardial infarcts in 5 hearts in syphilitic aortitis. In 2 the infarcts were the result of syphilitic changes in the aorta and at the mouths of the coronary arteries, and in 3 they were caused by concomitant coronary atherosclerosis and thrombosis. She stressed the histologic similarity between very recent infarcts (as indicated by the presence of polymorphonuclear leukocytes) and the "malignant syphilitic myocarditis" of Warthin.

Jaffé (1946) believed that there is a form of diffuse "syphilitic" myocarditis which is not produced by spirochetes but by a local allergic reaction, as has been mentioned previously. He stated that the diagnosis can be made only in the presence of other syphilitic lesions in the body. He emphasized that this form of myocarditis is rarely observed in Europe and in the United States, but is frequent in Venezuela. He recognized three kinds of myocardial syphilis: (1) diffuse myocarditis; (2) gummatous myocarditis (microscopic gummata); and (3) gross cardiac gummata.

Gummata in the myocardium are rarely reported. Saplar (1932) reviewed the literature for their incidence. Clawson in 1941 found only 5 instances of gummata in the myocardium in 30,265 autopsies. Spain and Johannsen (1942) reported 3 cases of localized gummatous myocarditis. In 1 case the gumma had impinged on both the tricuspid and pulmonary valves, and in another case the gumma had invaded the posterior leaflet of the mitral valve. Kobernick (1947) reported a gumma of the coronary artery and a gumma of the heart. He stated that only 100 cases of gummata had been reported in the literature.

From the available literature and from personal studies, it must be concluded that the entity "syphilitic myocarditis," a diffuse syphilitic inflammation with the presence of spirochetes, in acquired syphilis, is extremely rare, if it occurs at all. This does not mean that the final word has been spoken, but it indicates the need for further exhaustive stud-

ies closely linked with the problem of syphilis in general. The hearts of syphilitic patients should be subjected to a careful search for microscopic lesions. Every method available for demonstrating spirochetes should be used. More thorough studies of the cultural characteristics of *Treponema pallidum* and animal experiments are essential, always having in mind the possibility of producing specific myocardial changes and taking into consideration the immunologic state of the host.

Weil's Disease (Infectious Spirochetal Jaundice). Mollaret and Ferroir (1935) reported an instance of fatal myocarditis in Weil's disease. They found swelling of the heart muscle nuclei and chromatolysis. The interstitial tissue was infiltrated by lymphocytes and polymorphonuclear leukocytes. In one region a necrotic focus was demonstrated. They particularly emphasized the extreme dilatation of the capillaries. Leptospirae were not found in the myocardium.

Viral Diseases

A number of reports have appeared of myocardial changes in diseases of viral origin. Experimental work with various viruses, identification of certain viruses in patients who subsequently died with myocarditis, and electrocardiographic changes in patients with well-known viral diseases have shown conclusively that myocarditis occurs in viral diseases.

Silber (1958) reported the clinical features in 21 patients with viral myocarditis. The diagnosis was based on serologic tests or was made presumptively by exclusion of other recognized etiology. Because of the paucity of reports of demonstration of the virus in the myocardium, he concluded that it is not necessary that the virus actually be located in the myocardium in order for the infection to induce the myocardial inflammation. He also remarked that only a few viruses produce morphologic lesions that are diagnostic.

While it is true that the tissue reaction in itself is not diagnostic, it has already been pointed out that isolated necrosis of individual muscle fibers adjacent to an inflammatory exudate seems to be the most characteristic

histologic feature of viral myocarditis. The mere fact that only a few cases have been recorded in which the virus was actually cultivated from the myocardium should not lead to the conclusion that myocarditis in viral diseases may occur in the absence of the virus in the myocardium. It should rather serve as a stimulus for more concentrated studies.

Helwig and Schmidt (1945) isolated a virus from a group of anthropoid apes that had died from interstitial myocarditis, and were able to produce myocardial lesions consistently in mice. Schmidt (1948) reported the isolation from a chimpanzee dying of interstitial myocarditis, of an agent that produced myocarditis and encephalitis in mice and hamsters and myocarditis in guinea pigs (virus of "encephalo-myocarditis"). He remarked that the morphologic findings in the heart duplicated, to a remarkable degree, the myocardial lesions found in human heart muscle in several viral diseases. He also suggested that isolated myocarditis of man (Fiedler's myocarditis) might be caused by a virus.

Warren (1948) found, in serums from 17 patients with so-called 3-day fever which occurred among Army personnel stationed in and near Manila, appreciable amounts of specific neutralizing antibodies for the virus of encephalo-myocarditis. In this connection, the work of Pearce and Lange (1947) may be pertinent. They found that the incidence and severity of myocarditis, in rabbits suffering from a variety of viral infections, are markedly increased when these animals are subjected to procedures that tend to decrease the amount of oxygen supplied to the heart.

Lyon (1947) emphasized that, from a clinical point of view, importance should be attached to viral myocarditis connected with epidemic infective hepatitis, infectious mononucleosis, yellow fever, varicella, dengue, poliomyelitis, atypical primary pneumonia, rubeola, measles, mumps and influenza-like infections. Because of the benign character of the majority of these diseases, myocardial involvement is usually overlooked. Ungar (1948) described "nonpurulent myocarditis" in acute epidemic encephalitis, the myocardium containing infiltrations mainly of lymphocytes and of relatively few polymorphonuclear leukocytes.

Poliomyelitis. Myocarditis is frequent in poliomyelitis. Saphir (1945b) found myocarditis in 10 of 17 patients who died of poliomyelitis. Histologically, the inflammatory

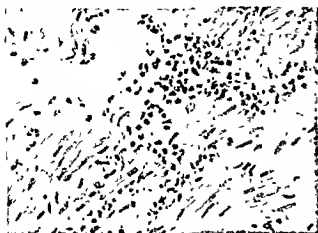


Figure X-60. Myocarditis associated with poliomyelitis. Patient died 12 hours after onset of symptoms. Note almost exclusive presence of polymorphonuclear leukocytes. Iron-hematoxylin. X 300.

cells consisted principally of lymphocytes and neutrophils; occasionally diffuse infiltrations of polymorphonuclear leukocytes were noted. In patients dying within the first week of the infection, the myocardium showed many neutrophilic polymorphonuclear leukocytes (Figure X-60), sometimes massively invading the myocardium. Later more and more mononuclear cells appeared (Figure X-61). In patients dying 4 to 6 weeks after the onset of symptoms of poliomyelitis, the myocardium contained many lymphocytes and monocytes, principally in the interstitial tissue.

Among 35 autopsies of victims of poliomyelitis, Ludden and Edwards (1949) found myocarditis in 14. They pointed out that proof that the cardiovascular lesions in acute poliomyelitis are caused by the virus of poliomyelitis, will depend on the demonstration of the virus in the lesions and on the experimental production of such lesions. (See also Saphir and Wile, 1942.) Ludden and Edwards observed lesions similar to those which have been described in other infectious diseases and in Fiedler's myocarditis. They asserted that myocarditis should be suspected in every patient who is seriously ill with acute poliomyelitis. It is interesting to note that in one of their cases there was rupture of the right atrium, with resulting hemopericardium. Histologic study showed degenerative myocardial changes. The muscle fibers, particularly near the area of the perforation, showed loss of striation and few neutrophils. Dolgopel and Cragan (1948) found focal myocarditis in 16 of 92 cases of poliomyeli-

tis. The incidence of myocarditis in 45 cases, in which multiple sections from each heart were available, was 26.6 per cent. They thought that cardiac failure was the immediate cause of death in at least 4 patients. From the evidence at hand, it seemed probable that these lesions were produced by the virus which caused poliomyelitis. Whether or not this assumption is correct, it is apparent that myocarditis occurs frequently in poliomyelitis. Spain and associates (1950) found myocarditis in 12 of 14 patients with poliomyelitis. It is noteworthy that in one of these the myocarditis was diagnosed clinically. They believed that the myocarditis was caused by a virus. Abnormal electrocardiograms were found by Laake (1951) in 31 per cent of patients with poliomyelitis, and by Ulfacker (1954) in 21 of 92 children with the disease. Jungeblut and Edwards (1951) isolated the virus of poliomyelitis from the heart of 2 patients with poliomyelitis, thus proving that the myocarditis was actually caused by a virus.

The *encephalomyocarditis virus* is apparently also responsible for disease in man. Koch (1950) was able to demonstrate an infectious agent (virus) in the blood serum of 1 patient, in the cerebrospinal fluid of a second, and in the blood serum and feces, and in the liquid that was used to wash out an ear in a third patient. Neutralizing antibodies were found in the serum of patients who recovered. This virus produced convulsions and paralysis when injected in mice and rodents. In the patient who died, autopsy disclosed interstitial myocarditis, but the brain was not examined. Koch believed that this virus belonged to the encephalomyocarditis group of viruses. Saphir (1952) reported 3 instances of infection presumably caused by this virus. For a historical review of this virus, see Gajdusek (1955).

Myocarditis has been found associated with *Coxsackie virus* infections, as in Bornholm's disease. This virus is closely related to that of encephalomyocarditis. Epidemics of this disease have been reported in maternity homes, and the virus has actually been isolated from the heart muscle of a newborn infant by Javett and associates (1956). Microscopically, the myocardium has been seen to be infiltrated with large mononuclear cells, histiocytes and an occasional polymorphonuclear leukocyte.

Saphir and Cohen (1957) reported 5 instances of myocarditis in infancy which they thought was of viral origin because of necrosis of isolated

muscle fibers. Since 3 of these infants died shortly after birth, it appeared that the myocarditis was caused by a virus transmitted through the placenta. It seemed most likely that the virus belonged to the group of Coxsackie viruses. Because of severe electrocardiographic changes encountered in 1 of the infants shortly after birth, an anomalous origin of one of the coronary arteries was suspected.

Stoeber (1952) drew attention to various epidemics of myocarditis in infants, especially those occurring in 1937 and 1944 in Munich, Germany. Characteristically, this disease had a sudden onset and was attended by marked pallor, moderate cyanosis of the lips, and dyspnea. In a few cases in which electrocardiograms were taken, changes in the T waves were common. Siblings were relatively frequently involved. A causative bacterium could not be cultivated. Stoeber believed that this myocarditis was of viral origin, and pointed out that these cases should not be classified as isolated (Fiedler's) myocarditis because they are not principally interstitial in nature. Early changes were found in the muscle fibers and nuclei, culminating in abnormal forms of nuclei

and in necrosis of muscle fibers without fatty degeneration. Somewhat later, there was interstitial round cell infiltration which was believed to be secondary to the parenchymatous changes. Still later, there was severe degeneration of the parenchyma with large foci of fibrolysis, followed by proliferation of connective tissue replacing necrotic muscle fibers.

Song and Sprunt (1958) described nonbacterial pancarditis which morphologically was identical with isolated or diffuse interstitial myocarditis of unknown etiology, in each of 3 patients who had a moderate degree of interstitial pneumonia. These cases probably also fall under the heading of viral myocarditis, especially since the accompanying microscopic pictures disclose necrosis of individual muscle fibers.

Influenza. Nonbacterial myocarditis has also been reported in influenza A infection in which the virus was isolated from the lungs. Cardiac disturbances, such as bradycardia, extrasystoles, partial or complete heart block, sino-nodal block, loss of various complexes and T wave changes in the electrocardiogram,

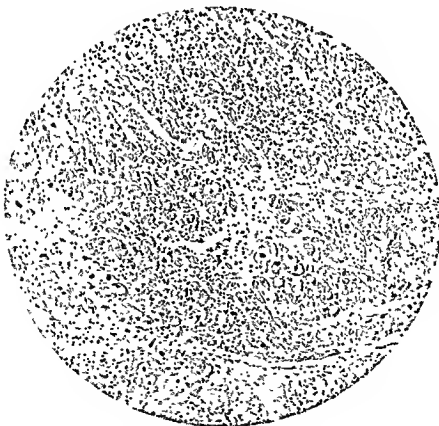


Figure X-61. Myocarditis in polomyelitis. The patient died late in the course of the disease. Hematoxylin and eosin. X100. (WCGH, 45 P 191 M.)

which may be observed after influenza, may be explained on the basis of myocarditis.

Finland and associates (1915) reported 2 such instances in which they found necrosis of muscle fibers with extensive infiltration of lymphocytes, plasma cells, large mononuclear cells, and occasional eosinophils and mast cells. They emphasized that a prolonged and diligent search had been made for evidence of myocardial damage. Inflammatory changes in the myocardium have also been reported by Binford and Hanver (1941) in severe pneumonitis, in which minute coccobacillary inclusions were encountered in a few alveolar lining cells, in a few cells of the alveolar exudate, and in one Kupffer cell in the liver. Microscopic examination of the myocardium disclosed a few clusters of mononuclear cells distributed around interstitial capillaries and larger vessels. Lustok and associates (1955) found myocarditis in 9 patients with viral pneumonia.

Infectious Mononucleosis. Lyon (1916) reported acute myocarditis with electrocardiographic changes in the terminal deflections of the chest lead, as a sequel of infectious mononucleosis. A detailed study by Custer and Smith (1948) disclosed changes in the myocardium in 6 of 8 autopsies of patients with infectious mononucleosis. Aggregates of lymphocytes were sparsely distributed within the myocardium about small blood vessels. They were also present in small numbers beneath the endocardium. In only 1 case was the reaction virtually negligible. In another, the cellular infiltrate was rather prominent. Allen and Kellner (1947) emphasized the finding of a few interstitial collections of mononuclear cells and lymphocytes of moderate size.

Fish and Barton (1958) reported cardiac involvement in infectious mononucleosis in a 20-year-old man. The electrocardiographic changes were severe. Microscopically, the interstitial tissue of the myocardium was infiltrated by large round cells which resembled lymphocytes, and necrosis of individual muscle fibers was also demonstrable.

Rubeola (Measles). Degen (1937), in a study of 100 fatal cases of measles, found pericarditis in 4. In 2 there was a shaggy exudate on the visceral pericardium and the pericardial sac was distended with purulent fluid, while in 2 there were lesser amounts of purulent fluid and no fibrinous exudate. Pericardial effusion was somewhat more common, effusion of clear fluid being noted 23 times. The heart itself showed no char-

acteristic gross changes. Dilatation of the right side of the heart was found 21 times. Of 91 hearts examined microscopically, only 4 showed more than the usual toxic changes. These 4, including the 2 with exudative pericarditis, had cellular infiltration in the myocardium. The infiltration was chiefly lymphocytic and was partially, but not predominantly, perivascular. Warthin (1931) described, as the essential lesion of the prodromal stage of measles, a subepithelial infiltration of multinucleated syncytial giant cells, lymphocytes and monocytes in the tonsils and pharyngeal mucosa. Since this discovery there have been several reports of autopsy findings in measles, notably those by Minami (1938) and by Semroth (1939). Neither of these investigators mentioned any changes in the myocardium. Acute arrhythmias and electrocardiographic changes in a patient with measles were recorded by Gindra (1951). When the patient died 3 years later, generalized myocardial fibrosis was found. From the scarcity of pertinent literature it must be concluded that true myocarditis is rare in measles. Complete heart block occurring during the preinfective stage of *rubella* (German measles) was reported by Logue and Hanson (1915).

Epidemic Parotitis (Mumps). In 1918 Pujol (*Arch. de méd. et pharm. mil.*) observed clinical evidence of myocarditis in patients with mumps. He noted the absence of previous histologic studies of the heart in mumps.

Wendkos and Noll (1914) claimed to have described the first known case of myocarditis complicating mumps in which the diagnosis was established during life. Rosenberg (1945) reported complete heart block in 2 patients with epidemic parotitis. Among 101 consecutive patients with epidemic parotitis, evidence of myocardial involvement was observed 16 times (15.4 per cent). In all but 2 patients, the electrocardiographic changes were transitory. Felkner and Pullen (1946) reported clinical and electrocardiographic evidence of myocarditis complicating mumps. No other etiologic cause for the myocarditis could be determined. In an analysis of a 4-year epidemic of mumps, Eagles (1947) encountered questionable myocarditis 3 times among 1664 cases reviewed.

Manca (1932) reported a singular instance of myocarditis with mumps. The patient was a 21-year-old soldier who contracted the disease during a severe epidemic in the barracks and died unexpectedly. The myocardium grossly was yel-

low-pink and opaque and was likened to boiled meat. Histologically, a serous and cellular exudate was seen, consisting of polymorphonuclear leukocytes, some lymphocytes, plasma cells and young fibroblasts. In addition, large cells were present with much cytoplasm and round nuclei the chromatin of which formed a coarse network; there was also cloudy swelling of the muscle fibers. Bacteria were not seen in the section.

Other Diseases. In yellow fever, myocardial degeneration is frequent but inflammatory changes are found only occasionally (Adler and Lyon, 1947). In experimentally produced yellow fever, outspoken myocarditis has been observed (Lloyd, 1931). Wood (1946) found myocarditis in early acute *epidemic hepatitis* complicated by spontaneous rupture of the spleen and fatal hemoperitoneum. Small groups of lymphocytes with occasional mononuclear phagocytes infiltrated the myocardium between the muscle fibers of the trabeculae carneae and also were prominent immediately beneath the endocardium.

Electrocardiographic changes with infectious hepatitis were also reported by Dehn and associates (1946). Among 6 fatal cases, myocarditis was found 4 times by Saphir and associates (1956). Areas of gross subendocardial hemorrhages may, on microscopic study, show foci of outspoken myocarditis.

Few reports are available of myocarditis in *varicella* (chicken pox) and in *variola* (smallpox). Hackel (1953) found myocarditis in 7 instances of *varicella*. Councilman and associates (1904) gave a classical description of the anatomy and histology of *variola*. In 4 cases, they found microscopically an interstitial cellular infiltration of large basophilic cells. One heart had general infiltration beneath the entire endocardium, but small foci of inflammatory cells were found elsewhere. Bras (1952) encountered foci of inflammatory cells in the myocardium in smallpox.

Dalgaard (1957) reported the unexpected death of a soldier 10 days following vaccination against smallpox. At autopsy, the myocardium was flabby, and microscopic sections showed foci of degenerated muscle fibers, necrosis of individual fibers and pronounced infiltration with granulocytes and lymphocytes. He believed that the myocarditis was caused by the cowpox virus (*vaccinia*).

Myocardial changes have also been described by Holz (1943) in *hoof-and-mouth-disease* in cattle.

Though *Friedreich's ataxia* is not considered a viral disease, it may be mentioned that Russell (1946) reported 4 cases in which *Friedreich's ataxia* was associated with a chronic interstitial myocarditis, 3 of the 4 patients having pronounced cardiac hypertrophy. Examination of the medulla oblongata failed to reveal any histologic abnormality in the region of the vagal nuclei. Russell argued that the myocarditis is of toxic origin, and in view of the known association between the nervous and cardiac disorders in *Friedreich's ataxia*, it is probable that the same agent is responsible for both lesions. Heymanick and co-workers (1949) reported changes in the electrocardiograms of 2 patients with *Friedreich's ataxia*. Autopsy performed on 1 of these disclosed diffuse myocarditis with fibrosis but no specific changes.

Myocarditis has also been reported in the *Landry-Guillain-Barré* syndrome, a disease entity of unknown but perhaps of viral origin. In autopsies of 50 such cases, Haymaker and Kernohan (1949) found 7 instances in which a mild focal myocarditis was observed, consisting of perivascular accumulations of lymphocytes, macrophages and Anitschkow cells.

A number of investigators have concluded that the myocardial lesions are caused by the actual presence of the virus. However, others maintain that it is difficult to assay the importance of the viral disease as the cause of myocarditis since bacterial infections are often found in fatal cases. Inasmuch as it has been shown experimentally that reduction of the oxygen supply to the heart markedly increases the severity of virus-induced myocarditis, it may well be that a complicating pneumonia, by decreasing the oxygen supply to the heart, serves to intensify the viral myocarditis in such patients.

Rickettsial Diseases

Typhus. Wolbach and associates (1922), in their extensive monograph, described inflammatory changes in the myocardium in typhus (Figure X-54). The characteristic lesions were nodular, were present most often in the inner half of the ventricular wall and consisted of collections of cells in which large ameboid and phagocytic mononuclears (epithelioid cells) predominated; lymphoid and plasma cells were numerous and mast cells and eosinophils were fairly common. Polymorphonuclear leukocytes were present in

TABLE X-17

Comparative Degree of Interstitial Myocarditis
in Scrub Typhus, Epidemic Typhus and Rocky Mountain Spotted Fever
(From Allen and Spitz, 1945)

Disease	Degree of Interstitial Myocarditis										Total No. of Cases
	0		+		++		+++		++++		
	No. of Cases	%	No. of Cases	%	No. of Cases	%	No. of Cases	%	No. of Cases	%	
Scrub typhus	5	7	32	44	27	35	8	11	2	3	74
Epidemic typhus	4	17	12	50	5	21	3	12	0	0	24
Rocky Mountain spotted fever	2	17	7	48	3	25		0	0	0	12

small numbers; they were more numerous if there was necrosis of muscle fibers. The necrosis usually involved only a portion of one or several muscle fibers. It was often impossible to recognize the obliterated blood vessels in these focal lesions. Capillaries filled with endothelial cells and frequently with fibrin thrombi were found in early lesions. A more diffuse infiltration of the myocardium was invariably composed of endothelial cells, lymphoid cells and plasma cells, which lay packed between capillaries and (apparently) normal muscle fibers.

In 97 per cent of 103 cases of typhus examined by Herzog and Rodríguez (1936), myocarditis was found which was described as "myocarditis exanthematica." This was characterized by sub-miliary perivascular nodules, consisting principally of adventitial cells, fibroblasts, lymphocytes, polymorphonuclear leukocytes and plasma cells. Often the polymorphonuclear leukocytes predominated.

Settle and associates (1945) reported autopsy findings of 55 patients with scrub typhus (*tsutsugamushi* disease) occurring in American troops in British and Dutch New Guinea and adjacent islands. Grossly the heart exhibited relatively mild changes and contained minute, focal, pale, brown-gray areas of degeneration or, more rarely, small recent focal hemorrhages. Microscopically, the dominant lesion in all cases was acute nonsuppurative myocarditis, focal as well as diffuse, which varied in severity. It was characterized by perivascular infiltration of mononuclear cells, plasma cells, occasional lymphocytes and polymorphonuclear leukocytes. Some times large multinucleated cells with vesicular nuclei and basophilic cytoplasm were encountered. Frequently the vascular endothelium was swollen or thickened by proliferating lining cells, recent

mural thrombi overlapping the endothelium. Allen and Spitz (1945) reported a comparative study of the pathology of scrub typhus (*tsutsugamushi* disease) and other rickettsial diseases. Table X-17, taken from their study, shows the comparative degree of interstitial myocarditis in scrub typhus, epidemic typhus and Rocky Mountain spotted fever. From the table, it appears that myocarditis is often encountered in these rickettsial diseases. Seemingly, it occurs more often and in a more severe degree in scrub typhus. They found no evidence that the right side of the heart was involved more frequently than the left side, that the ventricles were more severely damaged than the atria, or that one part of the wall of the ventricle was selectively involved, as has been stated by previous investigators. However, they emphasized the uneven distribution of myocarditis and that in some sections the plasma cell may be the predominating cell, in others the acidophilic macrophage, and in still others from the same case, the Anitschkow myocyte. Giant cells were also present. Polymorphonuclear leukocytes were encountered more often in *Rocky Mountain spotted fever*. The infiltrations were located principally between the muscle fibers, although they were also found in the periarterial fibrous tissue and rarely within the sarcoplasm of muscle fibers. Only exceptionally was there found an isolated, swollen, partially hyalinized fiber, the sarcoplasm of which contained one or two karyorrhectic inflammatory cells. The myocardial fibers were usually well preserved. In scrub typhus obvious fibrinoid degeneration of arteries of the heart was not found, but such a change was occasionally encountered in the other types of typhus. Necrotizing arteritis, however, was seen in 4 (17 per cent) of the cases of epidemic typhus. Involvement of the mural endocardium by mononuclear infiltrates was often striking in scrub typhus.

In a postmortem study of 31 cases of scrub

typhus, Levine (1946) found the principal cardiac changes to be in the myocardium. He described necrosis of the heart muscle fibers in about one-half of the cases showing carditis. However, he emphasized that necrosis was rarely severe. The essential pathologic response to the infection consisted of endothelial proliferation and infiltration with perivascular lymphocytes, plasma cells and many mononuclear cells.

Schopper (1943), who studied the material obtained by the Germans during World War II, also described extensive interstitial myocarditis in typhus. Among 70 cases of typhus, myocarditis was severe in 19, moderate in 14, and slight, principally interstitial, in 19, myocarditis was not found in the remaining 18.

In *Q fever* myocarditis was reported by Wendt (1953).

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Parasitic Diseases of the Heart

WALTER A. STRYKER

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LESIONS OF THE HEART resulting from parasitic (protozoal and helminthic) infection may be specific, by virtue of the presence of the parasitic agent within the tissues of the heart or pericardium; or nonspecific, the changes being secondary to the presence of the parasite in an adjacent or distant site. In some parasitic diseases, cardiac lesions are a major feature and upon their extent may depend the seriousness of the infection. In many types of human parasitic infection, no cardiac lesion has been reported.

Protozoal Infections

Amoebiasis. Amoebic involvement of the heart is a rare complication of amoebiasis. At least 45 proved cases have been reported in the literature (Carter and Korones, 1950, Norris and Beemer, 1956); in every instance, the lesion was an amoebic pericarditis. Usually it was secondary to amoebic disease of the liver (Kern, 1945).

In numerous other cases (Edwards, 1947) the patients have had cardiac symptoms or findings associated with intestinal amoebiasis or amoebic hepatic or pulmonary abscess, but definite proof of the amoebic nature of the cardiac lesion was

lacking. In one of the earliest reports of amoebic pericarditis by Howard and Hoover (1897), an amoebic (tropical) abscess of the liver was complicated by a fibrinopurulent pericardial exudate in which amoebae were found. The hepatic abscess did not actually rupture into the pericardium. Craig (1904) reported 2 cases of "acute pericarditis, resulting from perforation of an amoebic abscess of the liver into the pericardial cavity." In Clark's review (1925) of postmortem examinations of 186 patients with amoebiasis, no instances of amoebic cardiac involvement were found. Ochsenner and De Bakely (1943) found 1 example of amoebic pericarditis among 181 patients with amoebic hepatitis and amoebic hepatic abscess. They stated that less than 2 per cent of subjects with amoebic involvement of the liver have cardiac complications. They believed that such complications are more likely to follow amoebic abscesses of the left lobe of the liver, since abscesses in this lobe of the liver are more difficult to diagnose.

Coirault and associates (1955) likewise found that the left lobe of the liver was the usual source of the abscess rupturing into the pericardial sac, and that the pericarditis was usually fatal.

Grossly the parietal pericardium is thickened up to 5 mm. or more. The pericardial cavity contains a thick green-yellow purulent material which is usually adherent to both

pericardial surfaces. The surfaces are yellow-gray and granular. The usual landmarks are obscured. On microscopic examination, both the parietal and visceral pericardial surfaces consist of a thick fibrous connective tissue with surfaces covered by necrotic material. This material is backed by granulation tissue with numerous large mononuclear cells, occasional lymphoid and plasma cells, and sometimes also a few polymorphonuclear leukocytes. Individual or small clusters of amebae may be found in the necrotic tissue and also in the deeper layers of the pericardium. Typical is the small halo of cytolysis surrounding each ameba; phagocytosed red blood cells may be found within the parasite. The myocardium usually shows no change (Kern). It is not unusual to fail to find amebae in the fluid removed from a lesion which subsequently proves to be amebic in origin. Ochsen and De Bakey found amebae in only 16.5 per cent of cases in which the contents of hepatic abscesses were studied. The parasites may remain within the wall of the cavity. (See Figure XI-1).

In many amebic infections, especially those with liver abscess in which there is no involvement of the pericardial cavity, the heart will show nonspecific changes, such as fatty degeneration and cloudy swelling.

Trypanosomiasis. Human trypanosomal infections are characterized by the development of two quite different diseases. African sleeping sickness is the result of infection by either *Trypanosoma gambiense* or *Trypanosoma rhodesiense*. South American trypanosomiasis, also known as Chagas' disease, is caused by *T. cruzi*. Cardiac lesions occur in both diseases; in sleeping sickness the major lesions are cerebral and the cardiac lesions largely represent a complication, while in Chagas' disease the myocarditis is as important as the cerebral lesions, and may be most important as a cause of chronic cardiac disease.

Cardiac lesions are found in infections caused both by *T. gambiense* and *T. rhodesiense*. As is true of the cerebral lesion, the changes in the heart are more acute and severe in the rhodesiense form (Hawking and

Greenfield, 1941). The heart is of normal size but is pale and flabby. Microscopically, inflammatory infiltrates are seen around the smaller blood vessels in the endocardium, myocardium and pericardium (Thomas and Breinl, 1905). The left ventricle is affected more frequently than is the right. The cells are chiefly lymphocytes and plasma cells, although eosinophils, mast cells and giant cells have also been described. Muscle fibers adjacent to the inflammatory foci frequently show loss of striations. Hemorrhages may be seen either perivascularly or between muscle fibers.

In the rhodesiense infections, serous pericarditis and edema of the myocardium are usually present. Trypanosomes may be found in the pericardial fluid; with Giemsa's stain a few trypanosomes are sometimes seen in the tissues, especially in the superficial epicardium. In the gambiense form a fibrous proliferation, largely perivascular, may be present beneath the endocardium or diffusely in the myocardium. Lesions similar to those found in man have been produced experimentally (Peruzzi, 1928).

The electrocardiographic changes in 38 patients with sleeping sickness were reviewed by Schyns and Janssen (1955). Arrhythmias were rarely observed. In 47 per cent of the tracings, however, the T waves and ST segments showed alterations.

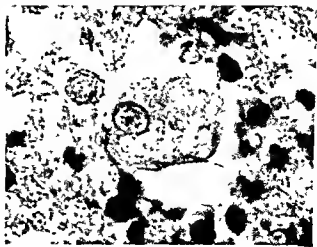


Figure XI-1. Trophozoite of *Endamoeba histolytica* (surrounded by inflammatory cells) in pericardial fluid. Paraffin-block section. Iron-haematoxylin stain. X 2400. (From M. G. Carter and S. B. Korones, *New England J. Med.*, 212:391, 1950. Courtesy of the authors and the editor.)

Chagas' Disease. South American Trypanosomiasis. The chief manifestations of South American trypanosomiasis are seen in the heart and the central nervous system. The organism localizes in the cardiac muscle fibers; rupture of these fibers causes a myocarditis, and the lesion may be sufficiently widespread through the heart to cause death. Both children and adults are affected. A report by Packchianian (1943) that the vector is present in certain portions of southern United States suggests the possibility that some cases of cardiac disease in these areas may be South American trypanosomiasis.

The clinical diagnosis is generally made by symptoms or signs of cardiac insufficiency, absence of heart disease of other apparent etiology, enlargement of both the right and left ventricles unaccompanied by hypertension, positive xenodiagnosis (demonstration of tritritinae of *T. cruzi* in fecal smears of laboratory-bred tritritomates about 40 days after they have been allowed to feed on the patient), and positive complement-fixation reaction for Chagas' disease.

The parasite is present in the blood as a trypanosome; when it enters the myocardial fibers it assumes a leishmanial form. The latter is round or ovoid and measures from 1.4 to 4 micra in diameter, and each contains a large ruby-red nucleus and a rodlike or spherical deep violet kinetoplast. Within the myocardial fiber multiplication of the parasite occurs by binary fission. The parasites are present in large numbers in the fibers; the parasitized fibers may be unaltered, hyalinized or fragmented (Crowell, 1923).

Parasitization of the fibers is not attended by inflammation, but upon rupture of the parasitized fiber, an inflammatory response usually occurs. The inflammatory infiltrate consists of lymphocytes, plasma cells, eosinophils and macrophages, and occasionally neutrophils (Johnson, 1938). Muscle fibers may be separated by edema. In addition, it may be difficult to find the parasites within the inflammatory foci. The organisms may penetrate other muscle fibers as leishmaniae, or may enter the blood stream as trypanosomes. (See Figure XI-2.)

Grossly, fibrinous pericarditis is often present, and the heart is pale; the myocardium may be flabby or firm. Punctate hemor-

rhages are seen and on section, yellow streaks or areas of mottling may be present.

The existence of a chronic cardiac lesion in South American trypanosomiasis is regarded as likely by many workers in countries in which Chagas' disease is endemic. In an important experimental study, Johnson (1938) produced active lesions in the dog, similar to lesions seen in man. In dogs that were allowed to live for several years, parasites could still be found within the myocardial fibers. The hearts of these animals also showed focal lymphocytic infiltrations and scattered areas of fibrosis. The fibrotic areas were most numerous in the myocardium adjacent to the endocardium and the epicardium, near the atrioventricular junction. These subendocardial foci of fibrosis may be the result of ischemia as well as of healing of an inflammation. Parietal thrombi may interfere with the nutrition of the subendocardial myocardium, and the resultant small infarcts may be followed by fibrosis. Such foci may be found especially at the apex of the left ventricle (Andrade and Andrade, 1955). Similar findings have been described by Decourt and associates (1947) in a person who was believed to have chronic Chagas' disease, and by Roinana (1947).

A positive epidemiologic history and a positive complement-fixation test served as the basis of a clinical diagnosis of chronic chagasic myocarditis by Rosenbaum and Alvarez (1955); in autopsies of 5 such cases, there was "disseminated myocarditis," but no parasites were found. Clinical findings included disturbances of cardiac rhythm, ectopic beats, nodal rhythm, and varying degrees of A-V block. The electrocardiograms were abnormal in 113 of 130 patients; the abnormalities included a right bundle branch block, ventricular extrasystoles, primary T wave changes, P wave abnormalities, and left ventricular enlargement.

Chronic Chagas' myocarditis may be complicated by pulmonary thromboembolism, secondary to right-sided cardiac parietal thrombosis (Rocha and Andrade, 1955).

Kuberle (1957) studied 100 cases of chronic Chagas' disease that came to autopsy. The diagnosis was based on demonstration of parasites in the myocardium (7 cases), positive complement-fixation tests (62 cases), demonstration of parasites and positive complement-fixation tests (11 cases), or on "characteristic" macroscopic and microscopic findings (20 cases). The gross findings consisted of hypertrophy and dilatation, fatty or hyaline degeneration and ischemic necrosis,

especially in the subendocardial portion of the apical regions of the ventricles. These changes, he thought, were the result of relative coronary insufficiency with ischemic changes, resulting in bradycardia and low blood pressure. Microscopically, parasites were sometimes found in the heart, most often in the wall of the right atrium, and usually after examination of a great number of serial sections. Granulomata were rarely found. Of principal interest was the occurrence of degeneration and liquefaction necrosis of the ganglia in the subepicardial tissue, often with complete loss of ganglion cells. The SA node, AV node and the region of the bundle of His showed fibrosis and infiltration of inflammatory cells. The author believes that in chronic Chagas' disease, the principal lesion is in the cardiac ganglia and in the conduction system, and that the resulting bradycardia and heart failure lead to "neurogenic" cardiac dilatation and hypertrophy. Koberle remarked that the mild destruction of the cardiac muscle contrasted with the severe destruction of the ganglia (supposedly by a neurotoxin of the parasites). He admitted, however, that the pathologic diagnosis of chronic Chagas' disease is extremely difficult.

Leishmaniasis. The leishmanial infections in man are of two types. *Leishmania dono-*

vani is the causative agent in kala-azar, which is characterized by visceral lesions. Cutaneous or mucocutaneous leishmaniasis is the result of infection by *L. tropica* (Oriental sore) or *L. braziliensis* (American mucocutaneous leishmaniasis). As might be expected, myocardial involvement has been reported only in kala-azar, and in this disease it occurs only occasionally. The essential lesion of kala-azar is the proliferation of the reticulo-endothelial cells in response to the presence of the parasite, and the heart is not an important site of these cells.

Meleney in 1925 reported a fatal infection of kala-azar in a man of 23. Autopsy revealed a suppurative pericarditis, in addition to the usual splenic, hepatic and other specific lesions. On microscopic examination of the heart, several areas of myocardial fragmentation were seen. In these areas were collections of inflammatory cells, including polymorphonuclear leukocytes, plasma cells, lymphocytes and clasmatocytes. Numerous Leishman-Donovan bodies were present within the clasmatocytes. No endothelial proliferation was noted.

Scattered foci of lymphocytes, polymorpho-

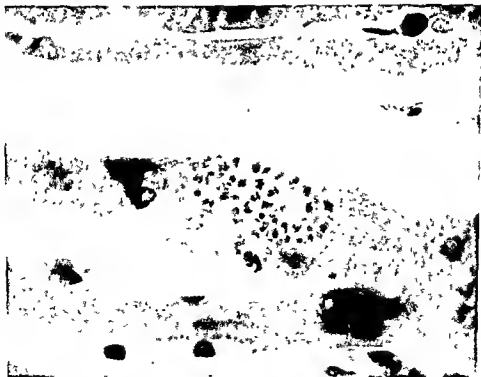


Figure XI-2. *Trypanosoma cruzi* in heart muscle. Iron alum, picric acid, hematoxylin stain. X 1285 (Courtesy of Morris Goldman, Communicable Disease Center, Public Health Service, Federal Security Agency, Atlanta, Georgia.)

nuclear leukocytes and macrophages have also been described (Luhitz, 1948) in cases in which no parasites were seen. The heart may be atrophic. While myocardial involvement may complicate the picture of kala-azar, it is not a major feature of the disease.

Malaria. All three forms of malaria, benign tertian (*Plasmodium vivax*), quartan (*Pl. malariae*), and malignant tertian (*Pl. falciparum*), show pathologic lesions related either to the phagocytosis of pigment by reticulo-endothelial cells or to the anemia resulting from destruction of the erythrocytes; falciparum malaria shows, in addition, lesions resulting from a concentration of parasites within the capillaries or organs, with plugging of these capillaries by the parasitized red blood cells.

Benign tertian and quartan malaria. The principal changes and serious tissue lesions in the "benign" types of malaria result from the anemia produced by destruction of erythrocytes. The anemia causes parenchymatous degenerative changes, including fatty changes in the heart (Dudgeon and Clarke, 1917; Sprague, 1946). Phagocytosis of pigment is seen mainly in organs rich in reticulo-endothelial cells; changes related to the presence of pigment in other organs may be seen in severe infections but never reach the intensity of those found in the spleen and liver. In human malaria, phagocytic cells are rarely encountered in the heart (Taliaferro and Mulligan, 1937). When present, they are usually seen within capillaries. The phagocytic cells are probably circulating leukocytes, although it has been suggested that some may be capillary endothelial cells which may become phagocytic in exceptional circumstances. The pigment consists of discrete yellow-brown or black granules of uniform size or of larger irregular agglutinated masses within the cytoplasm of the cells (Ash and Spitz, 1945). In chronic lesions, the pigment may form free masses, following destruction of the phagocytic cells. When present in sufficient quantities, a gross brown to black slaty color may be imparted to the affected organ. Blocks for section should not be fixed in formaldehyde because formalin-precipitated hemoglobin

may be confused with malarial pigment. Formalin pigment-granules are irregular in size and shape and are frequently crystalline.

Malignant tertian malaria. In addition to the pigmentation and the changes secondary to anemia, in falciparum malaria there are specific lesions caused by concentration of the parasites within the capillaries of the various organs. In general, the parasitized cells are uniformly distributed within the capillaries of such organs as the brain, heart, lungs and intestinal tract, which are not rich in reticulo-endothelial cells. The myocardial capillaries are distended with parasitized erythrocytes (Spitz, 1946). Ameboid forms of parasites may also adhere to the walls of the vessels and, at the bifurcations, clumps of ameboid forms may plug the lumen. Thrombi may be found in these vessels but are not always present. Parasites may also be found along the walls of larger vessels, particularly veins. The parasitized erythrocytes are often arranged as mounds which are present along the same side of the walls of different vessels, suggesting that some of the clumping observed in the vessels might represent a post-mortem phenomenon (Spitz). In the heart, varying degrees of changes within the individual myocardial fibers are found. In some cases there is no change; in others there may be loss of striations with translucency of the cytoplasm. Some cases have severe fatty degenerative changes, which may be diffuse or irregular, the fat being present chiefly as fine droplets. Interstitial edema is frequently seen and small areas of hemorrhage, either interstitial or subendocardial, are also encountered. In occasional cases in which there has been a high parasite count, an irregularly distributed interstitial myocardial infiltrate may be found; the cells include lymphocytes, plasma cells and macrophages. The plugging of the myocardial capillaries, with resulting anoxic changes in the myocardial fibers, constitutes a form of coronary occlusive disease (Merkel, 1946). The cause of the concentration of the parasites within the capillaries is not clearly understood.

The possibilities of hemoconcentration, agglutination of parasitized red blood cells, or the

presence of antibodies as factors influencing this phenomenon are discussed by Cannon (1941).

Malaria has not been proved to be a cause of chronic heart disease. Hyperplasia of collagen fibers and proliferation of young fibroblasts have been described in the "chronic malarial heart" (Galata, 1946).

Balantidiasis. A myocarditis caused by *Balantidium coli* was reported by Sidorov (1935). Histologically, *Balantidium coli* was found in the small arteries and within the myocardium. Foci of necrosis were bordered by giant cells of the foreign-body type, lymphocytes, a few eosinophilic cells and many fibroblasts.

Infections by Parasites of Undetermined Nature

Toxoplasmosis. Myocardial involvement has been observed in nearly half of the reported cases of toxoplasmosis (Callahan *et al.*, 1946). Next to the central nervous system, the commonest site of the infection appears to be the myocardium.

In a review of the literature, Hooper (1957) reported that pseudocysts and inflammatory lesions were present in the heart in 16 of 22 published cases of adult toxoplasmosis. In infants, lesions have been observed in the myocardium in 6 of 14 reported cases (Zuelzer, 1944). The parasites are found as agglomerations or as isolated organisms (Pinkerton and Weinman, 1940).

There is no true cyst formation but occasionally a thin limiting membrane derived from the adjacent parenchyma may be present. A clear space may surround the aggregate which is usually close to the nucleus of the fiber. The infected fiber is slightly swollen and may show partial loss of striations. The agglomeration varies in size, according to the number of individual bodies which compose it; its size and shape appear to depend in part upon the nature of the tissue in which it develops (Figure XI-3).

The largest masses occur in the cardiac muscle fibers and measure up to 50 by 10 micra. On the average, from 8 to 10 parasites are present but up to 60 have been observed. The individual organisms appear as crescentic, ovoid or rounded bodies measuring 3 to 7 micra in length and from 2 to 4 micra in width. Dimensions of indi-

vidual organisms vary; parasites that lie in loose tissue or are loosely packed are often larger than those found in denser masses. In transverse section the organisms are circular. The cytoplasm is clear, homogeneous and eosinophilic. The nucleus is fairly well demarcated from the cytoplasm, it is basophilic and may lie close to one end of the parasite. In fixed material the nucleus is often irregular in shape. The nucleus occupies nearly the entire width of the organism. In the myocardium there are also foci of necrosis, described as coagulation necrosis, with loss of myocardial fibers and infiltration of polymorphonuclear leukocytes, eosinophils and mononuclear cells (Paige *et al.*, 1942). Occasional parasites may be found in these necrotic foci. Parasites may be found in fibers at the periphery of the necrotic areas or in fibers at a distance from the necrosis.

The parasites are apparently able to invade the fibers of the myocardium without destroying them or producing inflammatory reaction in the surrounding tissues. The organisms divide by binary division until the myocardial fibers are completely filled. The myocarditis probably follows rupture of parasitized cells, the liberation of organisms inducing an inflammatory reaction in the surrounding tissue



Figure XI-3. Pseudocyst of *Toxoplasma gondii* myocardium of 12-day-old child. Cross-section. X-900. Note absence of inflammatory reaction about the pseudocyst. (Courtesy of Dr. Clyde Suartzwelder.)



Figure 11-4. Miescher's tubes, cut in cross-section, showing *Sarcocystis* from skeletal muscle of white rat X 150. (WCGH, 43 P 266)

(Callahan *et al.*, 1916). Other less prominent infiltrates of inflammatory cells may be scattered irregularly in the myocardium. Although in some instances the myocardial lesions are not severe, in other cases they are extensive enough to produce signs of myocardial failure.

The changes described above are those of fatal cases. In chronic asymptomatic toxoplasmosis, a few scattered aggregates of parasites have been described in the cytoplasm of the myocardial fibers (Tomlinson, 1915). No foci of necrosis are seen in these instances and there are no noteworthy cellular infiltrates.

Differential points in the histologic diagnosis of toxoplasmosis have been given by Pinkerton and Weinman (1940) and by Perrin (1943). Also of aid may be the isolation of *Toxoplasma* from heart muscle by animal inoculation (Paulley *et al.*, 1956). In a fatal case reported by Potts and Williams (1956), in which the clinical pathologic tests had indicated myocardial toxoplasmosis, no *Toxoplasma* organisms were found in more than 100 sections of the heart, but organisms were isolated by animal inoculation.

Hochrein (1957) advanced the theory that toxoplasmosis occurring during the first 8 weeks of pregnancy might cause congenital cardiac le-

sions. He reported 0 instances in which the mothers had a positive Sabin-Feldman test in titers ranging from 1:256 to 1:16,000, and eye-ground changes which were thought to be typical of toxoplasmosis. Four of the infants, ranging in age from 1 day to 5 months, came to autopsy; the other two, aged 8 months and 9 years old, were alive at the time of the report, and had clinical evidence of low ventricular septal defects. Hochrein did not support his findings by study of any control series.

Sarcosporidiosis. Cardiac involvement may occur in parasitization of man by *Sarcocystis*.

Gilmore and associates (1912) encountered 3 reports in the literature of human myocardial sarcosporidiosis. Their patient, an 11-year-old girl who died of malaria, was found to have 3 sarcosporidial cysts in the myocardium.

The organisms are found in cysts within scattered myocardial fibers. The cyst is an elongated oval mass measuring up to 0.19 mm. in length (Hewitt, 1933). Within a well-defined, often striated outer membrane are enclosed numerous individual basophilic bodies; many hundreds may be found in a fully developed cyst (Craig and Faust, 1951a). (See Figure 11-4.) Most of the parasites are round. In some instances no internal structure can be distinguished; in others, a nucleus with a central karyosome may be recognized. A difference may be noted between the central and peripheral parasites in a cyst, with the individual parasites separated into groups by prolongations from the cyst membrane. The outer compartments contain "round cells," while the inner fully developed compartments contain the characteristic crescentic bodies called spores. The dimensions of these spores vary widely in the reported cases, ranging from 2 to 16 micra. The involved myocardial fiber is usually slightly larger than the adjacent fibers. There is no necrosis or other evidence of reaction to the parasites. No cellular infiltrates are seen.

The organism must be distinguished especially from *Toxoplasma*; the location in muscle only, the lack of inflammatory response, and the large number of individual parasites within a true cyst are distinguishing points (Kean and Grocott, 1945).

Helminthic Infections

Trichinosis. Myocarditis is a frequent and serious complication of trichinosis, often resulting in cardiac failure. The myocardial lesions are caused by direct invasion of the myocardium by the circulating larvae. Following experimental feeding of trichina larvae to rats, trichina embryos were found in the myocardium as early as 5 days after feeding. There is a marked inflammatory response to the presence of the parasite (Figures XI-5 and XI-6). The latter either is destroyed or may be returned into the circulation. The larvae never encyst within the myocardium (Gould, 1945). Trichinosis does not produce any known chronic myocardial lesion or chronic heart disease.

Macroscopically, there are no constant findings. Parenchymatous degeneration of the heart may occur but this is nonspecific and may be related to nontrichinal lesions present at the time of death. The pericardial fluid may be normal or may be increased in amount; it may be clear or blood-tinged, and may contain one or more trichina larvae. The myocardium may be fairly normal in appearance or

may be pale; it varies in consistency from firm to soft and flabby. Occasionally, there is a yellow discoloration as a result of fatty changes.

Microscopically, the lesion is essentially an acute interstitial myocarditis which is focal in distribution. Some workers have found the lesion most marked just beneath the endocardium or epicardium (Gould, 1945). Areas of focal necrosis of myocardial fibers are surrounded by infiltration of inflammatory cells which include polymorphonuclear leukocytes, lymphocytes, macrophages, plasma cells and eosinophils in varying proportions. The myocardial fibers are often vacuolated. There may be scattered small hemorrhages and nonspecific degenerative changes.

The trichina larvae may be found within the foci of necrosis and leukocytic infiltration. Rarely a well-formed larva can be identified (Figure XI-5), while in other cases only fragments of one or more parasite undergoing destruction remain (Figure XI-6). The larvae measure from 80 to 120 micra in length and, in sections, show linear basophilic stippling. Larvae may be found in the heart as long as 54 days after infection (Stryker, 1947). With destruction of the larvae, the acute

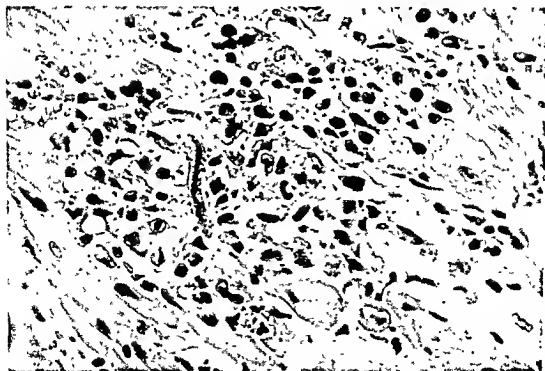


Figure XI-5. Larva in heart of white rat, 18 days after experimental infection. Note destruction of myocardial fibers and heavy inflammatory reaction. X:660. (WGGH, 53 P 690.)

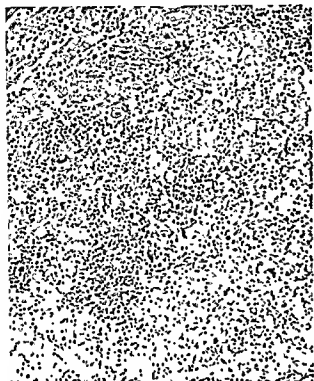


Figure XI-6. Trichinosis myocarditis. X 125. Note fragments of larvae undergoing destruction. Trichinae are unable to encyst in the heart (From Gould, S. E.: *Trichinosis*, 1945.)

inflammatory process subsides. It is possible that microscopic minute foci of fibrosis may remain as a result of this inflammation.

Laboratory findings of value in the diagnosis of trichinosis include eosinophilia in the peripheral blood, and electrocardiographic changes (Roehm, 1954). The latter include low voltage and inversion of the T wave, with later reversion to normal. Electrocardiographic studies indicate that the myocarditis is of maximal intensity during the seventh week of the illness. Roehm also found that the erythrocyte sedimentation rate was normal in the majority of cases. The infection often responds favorably to treatment with ACTH (Roehm, 1954; Segar *et al.*, 1955)

Trichuriasis. In man, infection by *Trichuris trichiura*, the whip-worm, is practically always limited to the intestinal tract. The only effects upon the heart would be secondary and these are usually lacking since the intestinal infection is relatively asymptomatic.

Getz (1945) believed that, in severe infections, prolonged diarrhea and anemia may eventuate in cardiac failure and death.

Capillaria hepatica. In a proved case of

massive infestation with *Capillaria hepatica* in a 7-year-old child (Otto *et al.*, 1954), the heart at autopsy was enlarged. The myocardium contained foci of large mononuclear cells which lay parallel to swollen collagen fibers adjacent to small blood vessels. The lesions were somewhat suggestive of Aschoff bodies. Similar lesions were seen in the left atrial endocardium. No parasites were found within the myocardium, and thus definite proof that these myocardial lesions were caused by the parasitic infection is lacking. *Capillaria hepatica* is a common nematode of rats, belonging to the same family as *Trichuris trichiura*.

Strongyloidiasis. Although the filariform larvae of *Strongyloides stercoralis* circulate in the blood stream before escaping into the pulmonary alveoli, the presence of the parasite elsewhere than in the respiratory and alimentary tracts is rare. Froes (1930) found rhabditiform larvae in the pericardial fluid of a 40-year-old man who also had massive pleural effusion containing larvae. The presence of rhabditiform larvae suggests that the patient harbored adult worms in the pulmonary tissue, as may occur in some cases of strongyloidiasis.

A report of myocardial lesions specifically caused by *S. stercoralis* has been given by Kyle and associates (1948).

A 47-year-old man with known strongyloidiasis had shown electrocardiographic changes, interpreted as being caused either by myocardial damage or by some extracardiac condition. No gross abnormalities of the heart or pericardial cavity were noted. Sections of the heart, however, showed scattered filariform larvae surrounded by focal accumulations of lymphocytes in the pericardium and in the interstitial tissue of the myocardium.

A pericardial location of larvae has also been reported in a chimpanzee by Blacklock and Adler (1922). Such isolated reports only emphasize the rarity of cardiac complications of strongyloidiasis.

Hookworm Disease. The cardiac lesions in patients infected with hookworms are non-specific. There is no report in which either the adult worm or its larval form has been

found in myocardial or pericardial tissues. The gross anatomic change in the heart that is associated with hookworm disease is cardiac enlargement. This change is caused by one of three factors: a reducible dilatation, a dilatation and hypertrophy, or a hypertrophy unassociated with a reducible dilatation (Porter, 1937). The chief factor in this cardiac lesion is believed to be anemia resulting from mechanical loss of blood from the intestinal tract at points of attachment of the adult parasites. The changes in the heart are the same as those seen in other types of anemia in man and in anemia induced experimentally. The primary cardiac dilatation is a physiologic adjustment which disappears when the anemia is relieved, if the factors continue, hypertrophy results. The changes are found both in the left and the right ventricles. Murmurs present may be partially hemic but also may be the consequence of a relative mitral insufficiency or a functional supravulvular pulmonary stenosis.

In a series of cases of cardiac enlargement associated with hookworm infection, 90 per cent of the patients showed relief of signs of cardiac involvement paralleling improvement of the erythrocytic and hemoglobin levels, in these patients, the intestinal hookworm infestations were persistent and untreated (Heilig, 1942). The remaining patients showed no change in the pathologic heart condition before deworming; in these cases, the heart dilatation and other myocardial signs improved quickly after elimination of the parasites. For this reason, it is postulated that there is a second pathogenic factor which is dependent on the presence of the adult worm. It is questioned whether this second factor is a toxin or an allergen; the eosinophilia characteristic of hookworm disease might indicate the latter.

Boccardelli and Rossi-Espagnet (1955), described electrocardiographic changes in 9 patients with hookworm disease. The alterations included depression of the ST segment and low voltage; and preterminally, diphasic T waves, extrasystoles and conduction disturbances of atria and ventricles. Some of the alterations subsided as the anemia improved.

Nonspecific microscopic findings have been reported in the hearts of patients infected with hookworms (Sanabria, 1945). These findings include interstitial edema, fatty and parenchyma-

tous degeneration of myocardial fibers, local and diffuse foci of polymorphonuclear leukocytes, plasma cells and eosinophils, and small foci of fibrosis. In those hearts in which the enlargement has been present for a long time there is also hypertrophy of myocardial fibers. Hydropericardium has been described (Carrillo, 1946).

Ascariasis. Both larval ascariasis in the myocardium and adult worms in the cavity of the heart have been reported.

Adelson (1952) found coiled *Ascaris* larvae in the myocardium of a 27-month-old male infant who died following an operation. Grossly, the heart was dilated, and a mottled yellow-gray area was present in the anterolateral area of the left ventricle. Microscopically, the larvae were surrounded by an inflammatory exudate consisting chiefly of eosinophils. Other zones had multiple foci of necrosis with centers of debris and adjacent granulomatous reaction. Within the jejunum, numerous *Ascaris* eggs were found. It was thought that the larvae, after being transported from the lungs to the heart, were carried to the myocardium by way of a branch of the left coronary artery.

Boettiger and Werne (1929) found 2 *Ascaris* worms in the cavity of the right ventricle of a 65-year-old woman. It was thought that they had either developed in the blood stream between the portal circulation and the pulmonary artery or had migrated in an unusual manner.

Rabinovich (1957) reported the occurrence of 2 adult *Ascaris* worms within the right atrium and right ventricle of a 2-year-old child. One worm was surrounded by a thrombus which extended into the pulmonary trunk and occluded the left pulmonary artery. The upper lobe of the left lung was the seat of a hemorrhagic infarct. The other worm was also enclosed in a thrombus which extended into the right pulmonary artery and produced occlusion of the vessel. In addition, a liver abscess contained 2 worms.

Toxocara canis. The aimless migration through human viscera of larvae of certain round worms, for which man is not the definitive host, or the resulting localized inflammation has been called larval granulomatosis or visceral larva migrans (Karpinski *et al.*, 1956) or allergic granulomatosis (Brill *et al.*, 1953).

In the case described by Brill and associates,

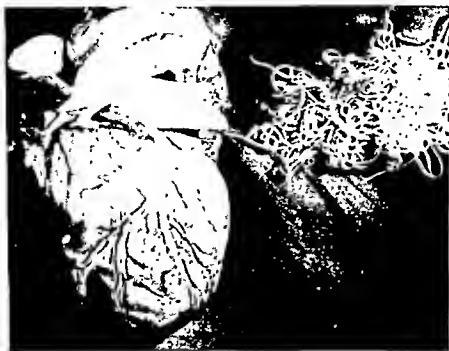


Figure XI-7 Heartworm (*Dirofilaria immitis*) infection in dog. (Courtesy, Armed Forces Institute of Pathology. Neg 108,784.)

granulomatous foci were found in the liver, kidneys, heart and lungs, and *Toxocara* larvae were demonstrated in the pulmonary lesions. In this case, the heart was dilated and, grossly, the myocardium contained small scattered nodules measuring up to 3 mm. in diameter. Microscopically, the nodules had dark eosinophilic centers containing chromatin debris and "fibrinoid" collagen bundles. Surrounding this were mononuclear cells of epithelioid type, with multinucleated giant cells. Peripherally, there were eosinophils, plasma cells and polymorphonuclear leukocytes. This "allergic granuloma" was often found in relation to blood vessels, frequently a small vein.

Toxocara canis is a common parasite of dogs and cats; the eggs are passed in the feces and when the eggs are ingested, the larvae are liberated in the intestines whence they migrate through the lymphatics or blood stream. In the dog or cat the larvae eventually reach the bronchial tree, trachea and pharynx and, when swallowed, again mature into adult worms in the small intestine of the animal. Since man is an abnormal host, the life cycle in him is incomplete. There is experimental evidence that larvae can remain alive for a year or more (Smith and Beaver, 1953). The clinical manifestations vary, depending upon the total number of larvae and their localization.

Acanthocheilonemiasis. Although patho-

logic studies in man infected with *Acanthocheilonemo perstans* are lacking, the related parasites in monkeys may be found in the pericardium and other serous cavities. The worms "sew" themselves into the serous membranes where they cause local irritation, often with a resultant fibrinous exudate (Craig and Faust, 1951b).

Filariasis. Two instances have been reported of cardiac involvement in man by the heartworm. The first instance was reported by de Magalhães in 1887. A single male and a single female filaria were found in the left ventricle of a boy. In 1941, Faust and associates reported finding a mature male filaria in the inferior vena cava of an elderly Negro woman who had always lived in New Orleans. In both cases, the infecting worm was identified as a member of the genus *Dirofilaria*. (See Figure XI-7.)

Nagasawa (1927) is reported to have found larvae of *Wuchereria bancrofti* in the hearts of 6 persons. Gerbaux and associates (1957) described filariasis associated with idiopathic cardiac insufficiency in 6 persons, 4 of whom came to autopsy. They believed that the cardiac manifestations may have been related to an allergic process, and to Löffler's endocardi-

tis (see page 765). Generally, there was rapid heart failure usually involving the right ventricle. In 3 patients the signs became apparent the day after a febrile episode. In 4 patients larval or adult *Loa loa* were demonstrated in the blood. They stated that, in previously reported cases, the anatomic findings included pericarditis with effusion, intraventricular thromboses, and parietal endocarditis resembling Löfller's endocarditis. de Magalhães (1887) found a mature male and a mature female filarial worm (*Dirofilaria magalhães*) in the left ventricle of a Brazilian boy. (See Figure XI-7.)

Schistosomiasis. Specific cardiac lesions in schistosomiasis may occur either as a result of localization of the larval or adult worm in the heart, or of infiltration of eggs which have been deposited by the adult worm at the usual intestinal or vesical sites. Metastatic localization of the eggs occurs in the liver chiefly, in the lungs and brain infrequently, and in the heart occasionally. A cardiac lesion secondary to pulmonary schistosomiasis is also described.

Localization of an adult worm within the heart has been reported (El Gazayerli, 1939). In a man of 24 years who had schistosomiasis of many viscera, an adult male worm was found in the circumflex branch of the left coronary artery. The worm appeared intact and lay free in the lumen. No eggs were present in the heart. The possibility was considered that the cercariae had developed into adult worms in the pulmonary vessels.

The lesions caused by deposition of eggs in the myocardium are essentially the same as those found in the intestines, urinary bladder and liver. Faust (1948) has described these lesions; microscopically, they present the picture of a pseudo-tubercle, with individual eggs as the centers of tissue reaction. Adjacent to the egg is an area of lipid and coagulation necrosis of local tissue cells. Around this zone of necrosis is an envelope of macrophages, epithelioid cells and giant cells; while infiltrating the area more peripherally are large numbers of eosinophils, plasma cells and lymphocytes, and occasional neutrophils. In the acute phase, the character of the cellular

infiltrate may vary; sometimes a higher proportion of eosinophils is found.

Tiny abscesses with necrosis have been described by Thomas and associates (1946). In one case these authors noted thrombosis and hyaline necrosis of arterioles and venules with widespread necrosis of the ventricular septal myocardium.

As the lesion becomes more chronic, there is infiltration of fibroblasts and fibrocytes. The end-result is a complete fibrotic encapsulation of the egg. During this process the egg has become nonviable and may eventually be calcified. The eggs are seen in the acute phase as oval eosinophilic masses measuring 35 to 70 micra, containing irregularly scattered coarse basophilic chromatinic material which is separated from the chitinous shell by a clear space.

The deposition of eggs in the myocardium, although reported several times, is nonetheless uncommon. Jaffé (1943) found only one instance of such deposition in more than 400 autopsies on patients with schistosomiasis; and in Hutchinson's discussion (1928) of the pathology of schistosomiasis, the heart was not mentioned.

Right ventricular hypertrophy (cor pulmonale) is another cardiac lesion resulting from human schistosomal infection. The lesion is frequent and is associated with chronic pulmonary arteritis resulting from schistosomal infection, or represents a complication of hepatic involvement. The passage of the eggs from the portal to the caval system, and thus to the lungs, is facilitated by the portal hypertension produced by hepatic cirrhosis (de Faria, 1954).

Cor pulmonale with gross dilatation of the pulmonary trunk is a frequent clinical finding in Egypt (Day, 1937; Clark and Grace, 1935; Bedford *et al.*, 1946). In 100 necropsied cases of Manson's schistosomiasis, de Faria found cor pulmonale in 5 per cent. Among cases with hepatic cirrhosis, the occurrence was 11.2 per cent. The ratio of incidence in females to males was 9:1. Using the technique of cardiac catheterization, El-Ramly and associates (1953) made a clinical and hemodynamic study of cardiopulmonary schistosomiasis. They, likewise, found that the cardiac changes occurred in infections with either



Figure XI-8A. Cysts of *Cysticercus cellulosae* in dog's heart. Ventral surface

S. hematobium or *S. mansoni*. The vascular lesions were more frequent in infections with *S. mansoni*.

The eggs reach the lungs as emboli from the normal habitat of the worms and become impacted in the pulmonary arterioles or escape from the capillaries into the alveolar spaces. In either instance, they form granulomatous pseudo-tubercles as previously described with the eventual formation of fibrous nodules.

de Faria (1954) also believes that the lesions may be caused by toxins or may represent an allergic reaction. The vessels involved by the granulomatous inflammation are chiefly arterioles, and the result is either a necrotizing arteriolitis or a constricting periarteritis. He found that fibrinoid thrombi may also be associated with the endarteritis. The pressure in the pulmonary arteries increases, with resultant hypertrophy of the right ventricle and development of arteriosclerosis of

the pulmonary arteries. In some cases, the pulmonary valves may become incompetent.

The existence of a chronic myocardial schistosomiasis has been reported, especially by Jaffé (1937). However, these studies lack anatomic verification of the specific nature of the myocardial lesion. Jaffé found eggs in the myocardium in only 1 of 400 autopsies. Electrocardiographic patterns observed in the various stages of the development of chronic pulmonary schistosomiasis have been described by El Sherif (1953).

Heterophyidiasis. Cardiac involvement in various types of intestinal heterophyidiasis has been reported by Africa and associates (1935; see Craig and Faust, 1951c, d). The heart was involved by eggs of the following trematodes: *Heterophyes heterophyes*, *Metagonimus yokogawai*, *Haplorenchis yokogawai*, *Haplorenchis pumilio*, *Haplorenchis tatchui*, *Diorchotrema pseudo-cirratum* and *Heterophyes breviceca*. Clinically, the patients were in cardiac failure. Grossly the hearts were edematous and there were subepicardial hemorrhages, especially on the right side. The gross changes were similar to those of beriberi. Microscopically, the eggs of the various trematodes were found in spaces between cardiac muscular fibers and the capillaries were intensely injected. The interstitial tissues were edematous. Small pericapillary hemorrhages were believed to have been caused by rupture of the capillaries by the eggs. There was a lack of inflammatory and proliferative changes in these hearts. The authors believed the changes were the result of embolism of the eggs from the adult worms in the walls of the intestines.

An adult heterophyid has been found in the epicardial layer of the heart (Craig and Faust, 1951d).

Cysticercosis. When man is the intermediate host in infection with *Taenia solium*, the cysticerci may be found in any tissue of the body, including the heart. Localization in the heart, however, is unusual (Menon and Veliath, 1940). The cysts may vary from 0.5 to 3 cm. or more in diameter (Figures XI-8A and XI-B). They are usually multiple and may be located within the musculature or beneath the endocardial or pericardial surfaces. In general, they are round except in the deeper



Figure XI-8B Dorsal surface of heart. Note that some of the cysts have ruptured (Courtesy of Dr. Luis Mazzotti, Mexico City.)

portions of the muscle where they tend to be elongated. Around the thin glistening cyst wall, a pale thin fibrous capsule can be seen. The muscular bands appear to be separated by the cysts, and in some of the cysts the scolex can be recognized. Microscopically the cyst wall typically has three zones. The inner zone is composed of dead and disintegrating leukocytes and large mononuclear cells; foreign-body giant cells and foam cells may also be present; and occasionally cholesterol clefts may be seen. The middle zone shows fibroblastic proliferation and plasma cells. The outer zone contains vascular granulation tissue, polymorphonuclear leukocytes and a few eosinophils. The scolices may be well preserved or may show partial disintegration. Suckers and hooks may be perceptible. The

larvae may become necrotic and eventually undergo calcification.

Echinococcosis. The incidence of primary hydatid cysts of the heart is very low.

The Australasian Hydatid Registry includes only 6 cases of cardiac hydatid cysts in over 1800 cases of hydatid disease (Cole, 1947). In Iceland 2 instances of cardiac hydatid cysts were found in 60 cases of echinococcosis among 1200 autopsies (Dungal, 1946). Dew (1928) states that hydatid cysts of the heart comprise 1 to 1.5 per cent of all primary hydatid cysts. Peters and associates (1945) reviewed 61 cases of echinococcal infestation of the heart. They pointed out that echinococcal infestation of American cattle seems to be increasing, and that a similar increase may be present among sheep and hogs. This increase may well be reflected, sooner or later, in the ap-

pearance of human cases of echinococcal infection acquired in the United States.

Early recognition of cardiac echinococcosis is important since the lesion is amenable to treatment. Successful surgical removal of echinococcosis cysts has been reported (Stojanovic and Vujadinovic, 1955; Molloy, 1955). Larghero (1954) reported successful removal in 9 of 10 cases.

In a majority of cases hydatid cysts of the heart are primary, having developed from the hexacanth embryo. After the embryo has traversed both the hepatic and pulmonary capillaries, it is carried to the heart muscle by the coronary arteries (Dew). In some instances, attachment may be directly to the endocardial surface, with subsequent growth into the cardiac tissue. The embryo usually comes to rest in the muscle of the ventricle or atrium and the resultant cyst may grow toward the chamber of the heart or may project under the visceral pericardium. It is at first simple and may remain quiescent for a long time before some complication occurs, or it is discovered either on roentgenologic examination of the chest or at autopsy. Primary cysts are probably always solitary. Multiple cardiac and pericardial cysts have been described but it is almost certain that all these cysts are in reality secondary to the rupture of a primary cyst. The right ventricle has been most frequently infected, although the cyst may develop under the endocardium or pericardium or in the muscular wall of any of the cardiac chambers. Secondary cysts are much more common in the right side of the heart. Hydatid cysts are at first simple and univesicular with a well-defined adventitia which, however, tends to become thinned when the cyst projects into the endocardium or pericardium (Schroeder and Medoc, 1945). Death or degeneration of the parasite may occur and the contents of the cyst become caseous or inspissated. It is possible that healing may occur in this way. Usually, however, as a result of constant increase in the size of the cyst and of continual trauma of muscular contraction, spontaneous rupture of the cyst occurs either into the pericardium or into one of the chambers of the heart. Rupture occurs

more frequently into the right cardiac chambers; this has been related to the lower pressure found in these cavities. At the time of rupture of the primary cyst, death may occur from anaphylaxis resulting from sensitization to hydatid proteins. If rupture has occurred into a cardiac chamber, death may also occur from pulmonary or cerebral embolism by the liberated material. If death does not occur, secondary cysts frequently grow in the lungs or in other peripheral organs, especially the brain. These secondary cysts characteristically have approximately the same size.

About 10 per cent of all primary cardiac cysts rupture into the pericardial sac. As a result of this rupture, the brood capsules and scolices are shed into the pericardial cavity and are there implanted. Some are destroyed by an inflammatory reaction, with resultant thickening of the serous membrane and formation of adhesions. Others, however, survive and develop into secondary cysts which are multiple and are approximately of the same size. These cysts may become covered by a membrane continuous with the pericardium.

Following rupture of the primary cyst, it may undergo involution and fibrosis, but more commonly the rent in its wall becomes healed and daughter-cysts form from the residual germinal elements. Rupture of daughter-cysts usually causes sudden death.

Grossly, hydatid cysts vary in size from a few micra to 1 cm. or more in diameter. The adjacent parenchyma is compressed. The cyst itself has a chitinous wall; and it contains smaller cysts, the daughter-cysts, and brood capsules and hooklets which form the so-called hydatid sand. The daughter-cysts are thin-walled and frequently lie free within the cyst fluid. Microscopically, the compressed fibrous tissue of the organ, in which the cyst lies, forms an outer wall. The external portion of the cyst proper is an acellular laminated chitinous layer. Within this is the germinal membrane to which may be attached brood capsules containing the invaginated scolices. Hooklets may be found free in the fluid of the cyst. A foreign-body reaction may be found in the wall of the younger cyst; this has been related to leakage of hydatid fluid.

Pseudo-tubercles may also form around degenerated scolices.

The clinical, radiologic and electrocardiographic features of echinococcosis of the left ventricle have been reported by Canabal and associates (1955). The lesion is usually single and, according to these authors, is more frequent in the left ventricle, probably because of a relatively richer coronary circulation. X-ray films may reveal a localized bulge when the cyst is of sufficient size. Calcification may be present; it is

more frequently seen in hydatid cysts of the heart than in those of the lung. Fluoroscopy, kymography and angiocardiology may also be of aid. The electrocardiogram shows alterations of the T waves.

Sparganosis. *Sparganum proliferum* is a proliferating larva of a pseudophyllidean tapeworm, the adult form of which is unknown. These larvae have been recovered from the heart as well as from other tissues of man (Craig and Faust, 1951e).

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Injuries of the Heart and Pericardium by Physical Violence

ALAN R. MORITZ

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THE IMPORTANCE of injuries of the heart by mechanical violence lies more in the frequency with which they are the basis for claims of workman's compensation or accident insurance than in the frequency with which such injuries are actually sustained. Each year many persons become disabled or die of previously unsuspected, spontaneously occurring heart disease. Each year many persons sustain injuries of one kind or another. Quite independently of any cause-and-effect relationship, chance makes it inevitable that injury will frequently be followed by the de-

velopment of signs and symptoms of heart disease. In an overwhelming majority, the sequence is fortuitous. In some, the injury has created an episode of stress that brings to light previously unrecognized heart disease. In some, direct damage to the heart has been done by outside violence.

It is the purpose of the ensuing discussion to examine the circumstances in which the heart may be damaged by the direct or indirect effects of physical violence and to review the structural and functional manifestations of such damage.

THE DIRECT OR PRIMARY EFFECTS OF PHYSICAL VIOLENCE ON THE HEART

Penetrating Injuries

Force responsible for penetrating wounds of the heart usually reaches that organ in one of two forms, i.e., as a flying missile or as a slender rigid object. Bullets and shell fragments constitute the majority of the former. Slender rigid objects, other than knives, that may be responsible for stab wounds of the heart include the sharp end of a broken rib

(Figure XII-1), an ice-pick, a sharpened file, a stiff wire, a long pin or needle, a sharp splinter of glass, wood or metal, and others too numerous to mention. In the majority of penetrating injuries of the heart, both civilian and military, the external wound is anterior thoracic and lies in an area bounded by the clavicle above, the tip of the xiphoid below, the costochondral junctions of the sternum on the right and the anterior axillary line on

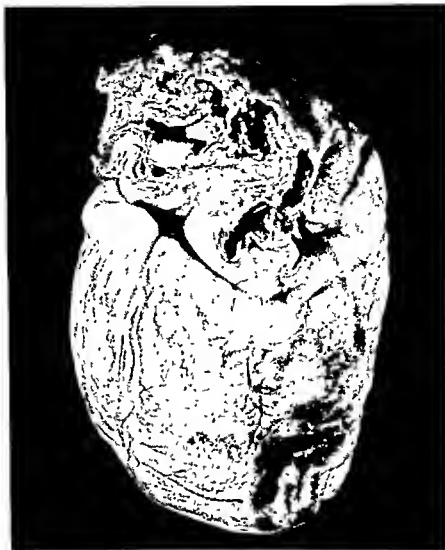


Figure XII-1. Stab wound of apex of right ventricle by end of broken rib.

the left (Hardt and Seed, 1942). The practical importance of this location with reference to the use of body armor by soldiers and other persons in similarly dangerous occupations is obvious.

One of the most significant factors in disruption produced by a bullet or by stabbing is the velocity of the object striking the heart. Ordinarily, a bullet travels at a much higher velocity than a knife and, hence, possesses more kinetic energy. Thus, a bullet that grazes or passes close to the heart is capable of liberating a great amount of energy to the tissues and often causes more extensive injury than would be expected from the size and course of the missile. It is not unusual for a heart, through which a small high-velocity projectile has passed, to be exten-

sively disrupted (Figure XII-2). Widely disseminated focal cardiac injury may result from the energy liberated by a bullet that has passed through the body in the vicinity of the heart.

A knife-thrust ordinarily occurs at relatively low velocity and its damaging effects tend to be local. Knife wounds of the heart, even though they are transmural, tend to close when the knife is withdrawn, whereas the passageway of even a small high-velocity bullet through the heart usually results in rapid and copious bleeding.

The remarkable propensity of the myocardium to effect partial closure of a transmural defect by its own turgor deserves emphasis. Hillsman (1947) observed in the case of small transmural wounds, both atrial and ventric-

ular, that the bleeding characteristically occurs in small spurts and only during systole. It is this phenomenon that often enables persons who have sustained penetrating wounds to survive long enough to have successful surgical repair of the defect. It also explains how persons with relatively large penetrating wounds of the heart are sometimes capable of astonishing physical feats prior to collapse and death.

Parmley and associates (1958) in a study of 456 fatal wounds of the heart and aorta found that approximately one in four survived the immediate effects of injury long enough to permit thoracotomy and surgical closure.

The consequences of penetrating wounds of the heart fall into three principal categories: dysrhythmia, hemorrhage and infection.

Dysrhythmia. Conduction disturbances

caused by disruptive cardiac trauma vary from such reversible and relatively insignificant phenomena as extrasystoles or bradycardia to almost immediately fatal asystole or ventricular fibrillation. Such functional disturbances are frequently out of proportion to the structural evidence of the injury.

Hemorrhage. The most common mechanism of disability and death following a penetrating injury of the heart is tamponade. If blood collects in the pericardial sac more rapidly than it can be evacuated through the defect in the pericardium, intrapericardial pressure eventually rises to such a height as to collapse the great veins, thereby preventing the return of blood to the heart (Figure XII-4). The time required for the development of tamponade varies from a few seconds to many hours, according to the rapidity



Figure XII-2. Large gaping wound in left ventricle produced by high velocity .22-caliber bullet.

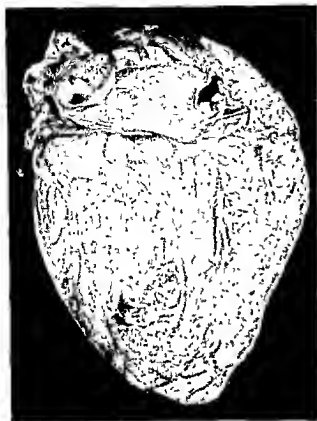


Figure XII-3. The epicardium has been lacerated by a bullet which grazed the posterior wall of the left ventricle. It required approximately six hours for sufficient blood (circa 400 ml.) to collect in the pericardial sac to cause fatal tamponade

of the bleeding and the patency of the defect in the parietal pericardium. The amount of blood that can be tolerated in the pericardial sac without tamponade probably varies considerably from person to person and tends to bear an inverse relation to the speed with which it accumulates. If the accumulation is rapid, not more than from 300 to 400 ml. can be tolerated (Figure XII-3). That larger effusions can be tolerated if the accumulation is slow is indicated by the occasional finding at autopsy of a hydropericardium containing as much as 1000 ml.

It should not be assumed that a penetrating wound of the heart is excluded by the absence of defect through the skin. Although any part of the heart may be damaged by the inwardly driven broken end of a rib, the right ventricle is especially vulnerable (Figure XII-1). Ordinarily the defect through the parietal pericardium in such circumstances is sufficiently large to prevent tamponade. This

is not invariably the case, however, because the end of a broken rib may rupture the ventricular wall through an intact parietal pericardium.

A clinically unsuspected organized intrapericardial hematoma is occasionally encountered at postmortem examination of the body of a person whose death occurred long after and from causes unrelated to the penetrating thoracic injury that caused the hemorrhage. Such observations tend to confirm the clinical impression that traumatic intrapericardial bleeding may cease spontaneously and without giving rise to clinically recognizable complications. Because of the frequency with which they believe that such bleeding does stop spontaneously and without surgical intervention, Elkin and Campbell (1951) have proposed that thoracotomy to control traumatic intrapericardial bleeding is usually unnecessary. They believe that aspiration of blood to prevent tamponade and to reduce the likelihood of infection is usually all that is required to deal with the situation. It should be noted that this proposal has not gone unchallenged. Griswold and Drye (1954), although agreeing that traumatic intrapericardial bleeding may stop spontaneously, suggest that it may be difficult or impossible to predict if this will be the case and that the safest procedure, therefore, is immediate thoracotomy for the suppression of further bleeding as soon as hemorrhage is suspected.

The absorption of extravasated blood from the pericardial sac by way of the lymphatics is exceedingly slow. The cellular components of the intrapericardial blood tend to organize at sites of mesothelial damage and may or may not result in adhesions between the surfaces. Pigment-containing macrophages may be found at the site of organized hematomas after many months.

If the defect in the parietal pericardium is large, death may result from exsanguination rather than tamponade. In such circumstances most of the escaped blood collects in the pleural cavities and the amount lost externally is relatively small.

Infection. Before the introduction of antibiotics, purulent pericarditis (Figure XII-5) was the most important complication of a penetrating wound of the pericardium, if the immediate effects of shock and hemorrhage were survived.

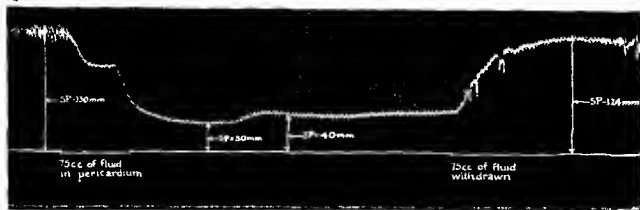


Figure XII-4 Cardiac tamponade produced within 30 seconds in dog by the injection of 75 ml. of saline into the pericardial sac. Systolic blood pressure (S.P.) fell from 130 to 30 mm Hg, owing to pressure on the great veins and atria. Four minutes later the tamponade was relieved by withdrawal of the saline solution and the blood pressure returned to normal.

Effects of Pleural and Pericardial Injuries on the Heart. Frequently, although not invariably, a penetrating cardiac injury will be accompanied by wounds of the pleura or lungs. If the immediate effects of the cardiac injury are survived, such wounds may lead to the development of pneumothorax or interstitial mediastinal emphysema, either of which may embarrass the heart by displacement or compression. Entrance of air into lacerated pulmonary veins may lead to coronary and cerebral air embolism.

Healing of Penetrating Injuries of the Heart. Hesse and Hesse (1924) have observed that the blood clot filling a traumatic myocardial defect, even though it be small, is slow to resorb or organize. Significant fibroblastic invasion of the margin of a myocardial hematoma, according to them, is not seen much earlier than a week. The formation of granulation tissue first occurs at the site of the epicardial defect and is seldom well developed under two weeks. Fibroblastic proliferation along the transmural portion of the tract is minimal. Although occasional multinucleated cells indicate a reactive hyperplasia on the part of the injured muscle cells, there is relatively little regeneration. After a month it is difficult to recognize the intramural portion of a penetrating cardiac wound except by the presence of small epicardial and endocardial fibrous plaques at the sites of entrance (Figure XII-6) and exit.

Foreign Bodies. The position of the bullet as disclosed by roentgenologic examination of a person who has sustained thoracic injury by gunfire may be grossly misleading in establishing the probability of cardiac injury.



Figure XII-5. Purulent pericarditis following the successful suture of a transmural ice-pick wound of the pulmonary conus.

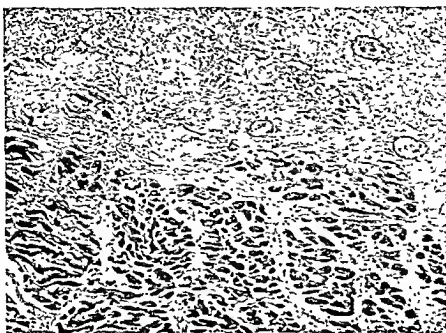


Figure XII-6. Subepicardial cicatrix at the site of a healed (many months) laceration of the wall of the left ventricle. Hematoxylin-eosin. X 100.

Bullets that have wounded the heart may strike the spine or a rib and ricochet to a remote position. Bullets that have entered the heart may be swept out of that organ by the systolic discharge of blood, to be carried into a pulmonary or peripheral artery. A bullet that has entered the precordium at an angle may strike a rib and ricochet to a position behind the heart without damage to that organ.

In 9 of 11 cases of intracardiac foreign body reported by Harken and Williams (1946), a bullet found in the right ventricle had first entered a systemic vein and had then been carried to the heart by way of the blood stream. In 2 instances bullets had been carried through the right chambers of the heart and had come to rest in a pulmonary artery. Although metallic foreign bodies situated in the pericardial sac or in the outer portion of the myocardium tend to become encapsulated by fibrous connective tissue and are often tolerated indefinitely without further disturbance (Figure XII-7), Harken and Williams believe that large foreign bodies (1 cm. or more in each of two diameters) within the heart constitute a potential hazard to health and life. Such a foreign body, according to them, may be mobilized as an arterial embolus

(pulmonic or systemic) or, if it remains within the heart, tends to predispose to the development of subacute bacterial endocarditis. Decker (1939) believes that the danger of migration, perforation and tamponade is an added reason for undertaking the surgical removal of a sharp foreign body.

Needles and similar pointed objects that enter any portion of the body and eventually migrate into a systemic vein may be carried to the right side of the heart. Here they may become embedded in the wall of the right ventricle or be carried through the chambers to become a pulmonary embolus. As an incidental postmortem finding, the author has seen (1) part of a hypodermic needle, that had been broken off in an arm many years before, embedded in an organized non-occlusive mural thrombus in a branch of the right pulmonary artery; and (2) a phonograph needle, that had entered the body at an unknown site at an unknown time, embedded in the interventricular septum (Figure XII-8). In both instances the foreign body had been tolerated without clinical evidence of its presence and without pathologic evidence of progressive injury.

A more important type of migrating foreign body is the sharp object that has been



Figure XII-7. Two lead shot that resided for 27 years in the wall of the right ventricle. There were no pericardial adhesions, no epicardial scars and no residual hematogenous pigmentation. Each pellet was enclosed in a thick fibrous capsule.

swallowed and that has penetrated the parietal pericardial sac by way of the anterior wall of the esophagus. The author has seen two such foreign bodies (a pin and a fish-bone) that had migrated in this manner and resulted in purulent pericarditis.

Blunt Injuries of the Heart and Pericardium

Of primary importance to a consideration of cardiac injury by blunt violence is the fact that during the first five decades of life the thoracic cage is usually sufficiently plastic to permit great distortion without fracture. Thus, an impact may produce severe injury of the intrathoracic viscera without damage to the ribs or sternum. In a series of nonpenetrating chest injuries (168 sustained by a fall from a height, 38 by the impact of a falling or swinging object, and 28 by a squeezing or

crushing force), Arenberg (1943) observed that the incidence and severity of cardiac injury were less in persons who had suffered broken ribs than in those whose thoracic cage was unbroken. It may be inferred that thoracic rigidity is an important factor in protecting the heart against injury by blunt violence.

Preliminary to a consideration of cardiac injury by blunt impact, it should be appreciated that hydrostatic forces transmitted to the heart by way of the great vessels may increase the bursting tension within that organ to the point of rupture (Figure XII-9). A crushing injury of the abdomen and lower extremities may displace blood toward the heart with sufficient force to rupture the intrapericardial portion of the thoracic aorta, lacerate valves or cause an explosive type of disruption of the wall of the left ventricle or atrium (Moritz, 1954). Cardiac injury caused by the application of blunt violence to the thorax falls into three groups, according to the severity of the disruptive changes: *commotion, contusion, and laceration*.

Cardiac Commotion. Cardiac commotion denotes a disturbance in cardiac function that has been caused by impact or agitation of that organ without the production of gross or microscopic evidence of injury. That the functional disturbance caused by an impact

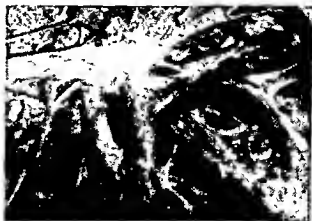


Figure XII-8. Phonograph needle projecting into the chamber of the left ventricle from a cicatrix in the interventricular septum. The needle had probably entered a systemic vein and had been carried in the blood stream to the right ventricle where it became embedded in and migrated through the interventricular septum.

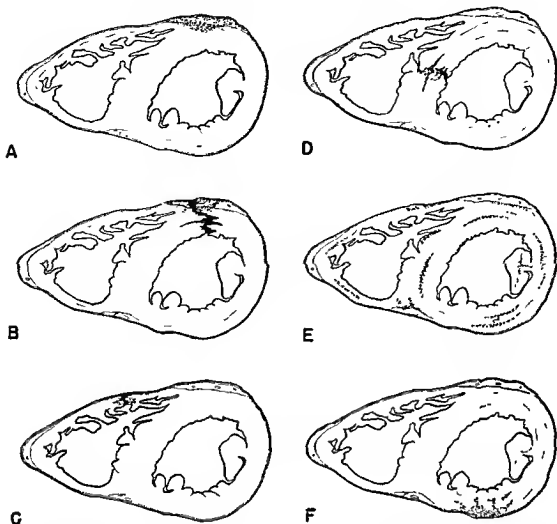


Figure XII-9. Various types of cardiac injury which may result from nonpenetrating thoracic impacts.

A. Anterior contusion,

B. Laceration of left ventricle,

C. Laceration of right ventricle,

D. Laceration of interventricular septum,

E. Disseminated non-communicating lacerations of myocardium,

F. Posterior contusion.

(From Montz, A. R. *Pathology of Trauma*. Philadelphia, Lea & Febiger, 1954. Reproduced by courtesy of publisher.)

to the heart may be disproportionate to the morphologic evidence of injury has long been recognized (Kulbs, 1909). It is a fact that a precordial impact may result in a severe and even a fatal disturbance in the function of what may appear to be an undamaged heart.

Without the benefit of a direct examination of the injured heart the clinical observer has no way of recognizing the extent to which the observed functional disturbance may be accompanied and explained by disruption of structure. Usually the most that can be said on the basis of history and clinical examina-

tion is that cardiac dysfunction developed immediately after, and presumably as the result of, an external impact. A posttraumatic functional disturbance of the heart that is transient does not indicate the absence of structural change, neither does one that is fatal require the presence of a visible structural lesion.

There is ample evidence from animal experimentation to support the conclusion that the force of a blunt impact to the chest may cause a wide variety of nonfatal or fatal disturbances in cardiac function without visible

evidence of injury (Kilbs, 1909; Schlomka and Schmitz, 1933, Bright and Beck, 1935, Kastert, 1939).

In a series of dogs in which the heart was exposed and subjected to nonfatal blunt impact, Moritz and Atkins (1938) found that structural evidence of cardiac injury was absent in 3 of 5 animals that developed posttraumatic extrasystoles, in 1 of 2 that developed bradycardia, in 2 of 6 that developed tachycardia and in 2 of 7 that developed ventricular fibrillation.

Since it is rarely possible to make a direct examination of the heart of a living person who has recently suffered a nonfatal cardiac injury, the frequency with which such transient posttraumatic cardiac disturbance occurs independently of structural lesions is not known. Transient posttraumatic disturbances in cardiac function in man following impact to the chest are not uncommon (Bright and Beck, 1935; White and Glendy, 1941; Barber, 1944). A few reasonably well-documented instances of death of persons resulting from heart failure following blunt injury of the chest, in which neither gross nor microscopic evidence of cardiac injury was disclosed by postmortem examination, have been reported (Warburg, 1938; Barber, 1944; Hedinger, 1944).

Certainly the evidence purporting to establish that the failure of an apparently uninjured heart has resulted from the direct effect of mechanical violence should be examined most critically. The requirement proposed by Kahn and Kahn (1929) that the signs and symptoms of cardiac dysrhythmia should develop immediately after the trauma in order to be consistent with a cause-and-effect relationship should be regarded as minimal.

The unreliability of the clinical diagnosis of traumatic heart disease, even though it qualifies as such under the relatively rigid criteria of Sprague (1947), is well illustrated in a case reported by Gore (1950). A young soldier not previously recognized to be suffering from heart disease sustained a blow to the chest which was followed by precordial pain, shock and tachycardia. On the fourth day of hospitalization, gallop rhythm and a precordial friction rub were heard. Death

from ventricular failure occurred on the seventh day. Postmortem examination disclosed that death resulted from subacute and chronic myocarditis which obviously had been present and asymptomatic for a considerable time before the occurrence of the injury. It was concluded that the traumatic episode had, at the most, acted as a trigger mechanism in precipitating the terminal illness.

The mechanism of traumatic dysrhythmia is obscure. Schlomka and Schmitz, and also Kastert, concluded from animal experiments that the cardiac disturbances caused by commotion are probably caused by reflex coronary vasoconstriction and myocardial ischemia. In support of this theory, Kastert reported the finding of focal areas of myocardial degeneration and necrosis in relation to the coronary termini in animals that had survived the immediate effects of a non-disruptive cardiac impact. Muller (1942) described disseminated foci of ischemic change in traumatized human hearts. Kartagener (1946), after a clinicopathologic study of the problem, doubted the occurrence of traumatic vasospasm unless the coronary arteries were already the seat



Figure XII-10. Explosive laceration of left ventricle due to hydrostatic force developed during impact from fall from height.



Figure XII-11. Diffuse interstitial extravasation of erythrocytes at the site of a posterior myocardial contusion. Death occurred several hours after blunt injury of chest. Hematoxylin-eosin. X 100.

of atherosclerosis. That coronary disease may increase the susceptibility of the heart to trauma receives some support from the early experiments of Külbs and Strauss who observed that rabbits having cholesterosis of the coronary arteries were less tolerant of thoracic impacts than normal animals.

Cardiac Contusion and Laceration. A *contusion* is a diffuse extravasation of blood into the interstitial spaces caused by impact (Figure XII-11). Minute vascular defects through which blood escapes may be created by excessive distortion or stretching of the tissue or by a sudden rise in intracapillary pressure because of the hydrostatic effects of sudden compression.

If only the heart is examined it may be difficult or impossible to distinguish between contusion and certain nontraumatic interstitial extravasations of blood. Subendocardial and subepicardial hemorrhage are frequently encountered when death has been preceded by an agonal period of asphyxia or anoxia or when death has been caused by some powerful systemic poison such as arsenic. Persons dead of hyperthermia frequently reveal spontaneous hemorrhages beneath the endocardium. If an interstitial extravasation of blood represents a contusion, it should be localized

to the heart and such other structures as were in the path of force, whereas if the bleeding was spontaneous and the result of a systemic disorder, it is not usually confined to the thoracic viscera. Another type of nontraumatic interstitial hemorrhage that may simulate cardiac contusion is an early infarct. The true nature of such a lesion is ordinarily disclosed by the finding of the occluded vessel and the presence of a central zone of ischemic necrosis.

A *laceration* is a gross defect in the continuity of tissue caused by a crushing or stretching force and, although it may or may not be associated with contusion, it is almost invariably associated with hemorrhage. An exception to this rule is a laceration of the chordae tendineae, inasmuch as these structures are normally avascular.

At first glance, it may be impossible to distinguish between traumatic rupture of the heart and spontaneous rupture from disease. Although the heart may be ruptured by a precordial impact, spontaneous rupture at the site of a recent myocardial infarct occurs more commonly. Should an infarct rupture, it usually does so within 3 to 10 days after its development. The true nature of such a lesion may not be recognized until either the site

of vascular occlusion is located or microscopic examination discloses changes indicative of antecedent necrosis.

Impacts responsible for disruptive cardiac injury are usually sustained over the precordium and may or may not be associated with fractures of the sternum or ribs. Helpern (1949), who has had extensive experience in the field of pathology of trauma, reported that he has never seen contusion or laceration of the human heart (or coronary arteries) as an isolated injury. He believes that the absence of objective evidence of extracardiac trauma justifies the conclusion that the cardiac lesion is probably nontraumatic. Although a fall from a height is the most common traumatic cause of cardiac rupture (Figure XII-10), a wide variety of trauma has been reported in the literature. Beck has emphasized the importance of the steering-wheel impact in which the driver is thrown forward by the sudden deceleration of his vehicle. It should be borne in mind that the object responsible for the fatal precordial impact may not be immediately recognized.

A man found dead on the floor of a factory was thought to have died of spontaneous cardiac rupture following infarction but at autopsy it was discovered that his cardiac lesion was undoubtedly of traumatic origin. It was subsequently learned that he had been working on a piece of wood, this had become jammed in a circular saw and was then hurled against his chest, causing immediate death. The piece of wood was later found at a considerable distance from the place where he had fallen.

Cardiac contusions and lacerations resulting from blunt injury may be anterior and directly beneath the site of the external impact or may be remote from it. Injuries from anterior thoracic trauma are sometimes found in the posterior wall of the heart, presumably as a result of impact of the heart against the vertebral column. According to Urbach (1922), the distribution of cardiac lesions resulting from blunt impact, arranged in order of diminishing frequency, are: right atrium, left ventricle, right ventricle, left atrium, interventricular septum, and valves.

The experimental findings of Moritz and

Atkins (1938) suggest that the hydrostatic force incident to sudden compression of the heart between the sternum and ribs anteriorly and the vertebral column posteriorly is a frequent cause of rupture. Lateral displacement of the heart by an obliquely directed force may lacerate the pericardium without damage to the heart or may tear the wall of the left atrium at the ostia of the pulmonary veins. In cardiac laceration incident to a fall from a height, partial or complete circumferential laceration of the aorta immediately above the aortic valves is sometimes encountered.

It has been observed both in persons and in experimental animals that a blunt injury of the heart may lead to widely disseminated myocardial hemorrhages without visible laceration. These are apparently the result of minute focal lacerations of muscle and probably result from an impact delivered while the ventricles are filled with blood. Both Munck (1937) and Warburg (1938) have stressed the frequency of this type of injury in human beings.

Posttraumatic Dysrhythmia. It appears that many if not most of the functional disturbances of the heart that have been observed in animals following blunt impact to the precordium may follow cardiac trauma in man.

In a series of experiments reported by Kulbs and Strauss (1932), bradycardia with extrasystoles was observed after single nonfatal impacts. In animals suffering from previously induced cardiac abnormality (aortic regurgitation, coronary arteriosclerosis, digitalis poisoning, thyroxine poisoning), the posttraumatic disturbances in rhythm were often accompanied by acute cardiac dilatation and terminated in death.

In experiments by Schlomka and Schmitz (1933) there were posttraumatic changes in the QRS and T waves and bundle branch block, the changes being similar to those which result from coronary insufficiency. The electrocardiographic disturbances were accompanied by a drop in arterial pressure, a rise in venous pressure, and right-sided dilatation. Bright and Beck (1935) exposed the heart in dogs and subjected it to direct impact of a metal hammer. There was often an immediate and extreme rise in pulse rate with falling arterial and rising venous pres-

tures. In experiments on survival, cardiac dilatation often persisted for several weeks. The electrocardiographic changes were similar to those reported by Schlomka and Schmutz, and their disappearance tended to parallel the reduction in size of the cardiac silhouette.

That a similar range of functional disturbances may occur in man following thoracic trauma is indicated by the numerous case reports included in the reviews written by Bright and Beck (1935), Glendy and White (1936), Warburg (1938), and Barber (1944).

Tamponade. Unlike the relatively slow bleeding so often observed after penetrating injuries of the cardiac chambers or of the epicardial vessels, hemorrhage following the type of cardiac laceration characteristically caused by blunt impact is usually so rapid as to be fatal almost immediately.

Myocardial contusions heal readily if the immediate functional effects of the injury are survived, and within a week the interstitial extravasation of blood is absorbed with little or no residual abnormality. The persistence of functional disturbances for more than a few days after injury should, in the absence of hemopericardium, cast doubt on the traumatic origin of the disturbance. An important exception to this generalization is the traumatically produced laceration of the interventricular septum. As pointed out by Cary and associates (1958), such an injury may result in chronic, progressive cardiac disability similar to that caused by a congenital interventricular septal defect.

Injuries of the Valves. The cardiac valves, their chordae tendinae and their papillary muscles, may be lacerated by precordial impact, by hydrostatic force transmitted from sites of trauma elsewhere in the body, or by the strain of overexertion. According to Glendy and White (1936), nearly all ruptured valves are found at autopsy to have been the seat of antecedent disease.

The largest series of traumatic rupture of normal valves is that reported by Adam in 1927 and includes 16 cases. Of these, 7 were of the aortic, 5 of the mitral, 1 of the aortic and the mitral, 2 of the pulmonic and 1 of the tricuspid. In 1925 Howard collected 112 cases of valvular rupture but this series included both diseased

and normal valves. White and Glendy (1941) have stressed the importance of being most critical of the evidence purporting to establish that a diseased valve has become insufficient because of trauma. Unless it can be shown that the valvular insufficiency developed after, and not before, the trauma and that the trauma or stress was of such a nature as to be consistent with the production of a disruptive force against the valves, the sequence in question should be regarded as unproved. If traumatic rupture of an atrioventricular valve is suspected, the heart should be opened with great care so as to avoid cutting the chordae tendinae.

Iatrogenic Injuries. The most commonly encountered iatrogenic cardiac injury is a puncture wound of the right ventricle sustained incident to the intracardiac injection of a cardiac stimulant. Occasionally sufficient blood escapes from such a wound to produce tamponade. Extensive contusion of the myocardium is seen commonly at postmortem examination of persons upon whom resuscitation by cardiac massage has been attempted.

Extensive myocardial laceration may be produced in this manner (Hurwitt and Seidenberg, 1953). Goodwin (1953) has called attention to the possibility of entangling the tip of a cardiac catheter in one of the columnae carneae of the right ventricle, with resulting damage to the underlying myocardium.

Since 1950 interest has rapidly grown in a unique type of cardiac injury sustained as a result of cardiac massage. In 1957 Adelson reported a study of the pathologic changes observed in the hearts of 60 persons, 44 of whom died during massage and 16 of whom survived cardiac massage for periods ranging from several hours to ten days. In 35 of the 60, the cardiac damage was characterized either as absent or slight, and in 25 as moderate or severe. An injury manifested by extensive subepicardial, subendocardial and myocardial hemorrhages was characterized as moderate. If gross laceration of a coronary vessel or of the myocardium was identified, the injury was characterized as severe. Although hearts containing old or recent infarcts were found to be particularly vulnerable to laceration, the severe injuries were not limited to this group. The author concluded that cardiac injury as result of massage was a function of technique rather than of the duration of the treatment or the presence of myocardial disease.

Injuries of Coronary Arteries and Veins. The functional or vasoconstrictive effects on the coronary arteries of force applied to the heart have been discussed in relation to cardiac commotion. Coronary vascular contusion and laceration remain to be considered.

Blunt injury. Although any coronary artery or vein lying in the path of force transmitted from a blunt impact to the precordium is theoretically capable of being bruised or lacerated, the vascular injury incurred in such circumstances is ordinarily a relatively insignificant feature of the total trauma. The larger epicardial arteries and veins are characteristically less vulnerable to injury by crushing, distorting or displacing forces than the tissue around them. A blunt impact to the chest of such violence as to cause bruising or laceration of a coronary vessel almost invariably produces concomitant myocardial damage of greater import.

In certain special circumstances the effects of trauma may be so sharply localized that vascular contusion is the most significant feature of the injury. Although it might seem plausible that coronary arteries and veins were equally susceptible to such trauma, the significance of venous lesions incurred in this manner is negligible.

Moritz and Atkins (1938) in experiments on dogs exposed the heart and delivered repeated blows over the descending ramus of the left coronary artery (Figure XII-9). The only instances in which recognizable vascular injury was sustained were in those experiments in which gross laceration of the myocardium occurred. Severe myocardial bruising was produced without appreciable damage to the coronary vessels lying directly beneath the site of impact. In unpublished experiments, Moritz observed that it was necessary to crush an artery between the jaws of a clamp in order to produce a localized vascular injury of sufficient intensity to result in thrombosis. Even in such circumstances the production of sufficient trauma to predispose to thrombosis is likely to result in the formation, first, of a false aneurysm as a result of the escape of blood into the wall of the vessel and, subsequently, because of free bleeding into the pericardial sac.

Thrombus formation in the lumen of the

damaged artery rarely results in occlusion and is characteristically confined to the mural defect, where it organizes as part of the reparative reaction.

The difficulties that have been encountered in attempts to produce traumatic coronary thrombosis in animals justify a most critical appraisal of the evidence when it is averred that such a thrombus has occurred in man. The facts (1) that active persons and particularly those engaged in physically arduous occupations frequently sustain thoracic impacts, and (2) that atherosclerotic heart disease is one of the most common causes of disability and death among the adult population, make it inevitable that many persons develop coronary thrombosis after sustaining some form of thoracic trauma. In most instances the sequence is fortuitous and not indicative of cause-and-effect relationship. We cannot exclude the possibility that blunt impact may in certain special circumstances produce, in an already diseased artery, sufficient localized injury to precipitate thrombosis. If coronary thrombosis is known to have developed within a few days after a severe precordial impact and if the site of thrombosis corresponds to the path of the transmitted force, the possibility of a cause-and-effect relationship needs to be entertained. If evidence of myocardial contusion or laceration in the vicinity of the vascular lesion is found at postmortem examination of such an individual, the possibility that trauma contributed to the development of thrombosis would be reasonably certain.

Thus, in a death investigated by the author, postmortem examination performed 5 days after the decedent had sustained a crushing injury of the chest disclosed a transverse fracture of the body of the sternum, hemorrhage throughout the anterior mediastinum, laceration of the parietal pericardium, contusion of the epicardium and myocardium over the upper anterior portion of the interventricular septum, recent thrombosis of the atherosclerotic proximal segment of the descending ramus of the left coronary and recent infarction of the tip of the left ventricle. Although it was not clear whether the thrombosis had occurred because of direct vascular injury or because of the state of the systemic circulatory

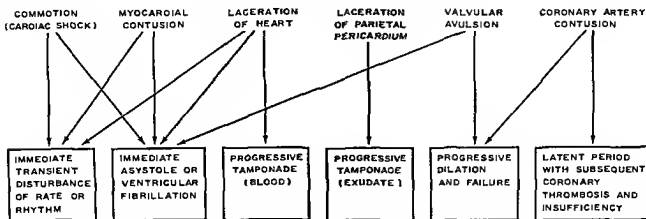


Figure XII-12. Direct injury of heart by blunt and penetrating injuries to thorax. (From Moritz, A. R.: *J.A.M.A.*, 156:1306, 1954, courtesy of the editor.)

stasis and shock which followed the injury, there was no reason to doubt a cause-and-effect relationship between trauma and thrombosis.

Traumatic Pericarditis. Earlier in this chapter attention was called to the occurrence of pericarditis as a complication of penetrating injury. Despite several clinical references to the occurrence of pericarditis with effusion following blunt injury, the author is in agreement with Helpert (1949) that there is no convincing pathologic evidence of such an entity. The escape of blood into the pericardial sac may cause pericarditis but if blood escapes into the pericardium as a result of blunt violence it does so because a chamber has been lacerated, and the patient rarely if ever survives such an injury for a period long enough to permit the development of pericarditis.

A typical illustration of the kind of clinical evidence cited in support of the concept of traumatic pericarditis is provided by a case reported by Ada and associates (1950). A man was kicked in the chest by a 3-year-old child and subsequently (2, 3 and 5 months later) had pericardial taps with removal on each occasion of approximately 400 ml. of old and recently shed blood. Because the patient stated that he suffered pain in the chest when he was kicked and because no

other cause of the bloody effusion was discovered, the pericarditis was designated as traumatic. While the nature of any injury that might have been inflicted by the child and the cause of these delayed and repeated episodes of intrapericardial bleeding are not clear, the traumatic etiology of the condition certainly cannot be regarded as established.

General Clinicopathologic Correlations. The various functional disturbances which may result from blunt and penetrating injuries of the heart are summarized in Figure XII-12 (Moritz, 1954). It should be noted that no clinical consequence of a nonpenetrating cardiac injury is pathognomonic of trauma. Although cardiac trauma may lead to the various disturbances that are indicated in Figure XII-12, the mere occurrence of such a disturbance following a thoracic injury does not of itself constitute proof that it was caused by the injury. In general, a functional disturbance of the heart that has been caused by trauma will almost invariably manifest itself almost immediately. The longer the interval between the occurrence of an injury and the subsequent development of signs or symptoms of cardiac disturbance, the less the likelihood that there is a cause-and-effect relationship between them.

THE INDIRECT OR SECONDARY EFFECTS OF PHYSICAL VIOLENCE ON THE HEART

Without doubt a heart already handicapped by a fixed reduction in the patency of its coronary arteries, or by severe myocardial or val-

vular disease is more likely than a normal heart to dilate and fail following the imposition of a sudden increase in work load. It is

doubtful that a normal myocardium ever sustains permanent injury as the result of exertion or excitement. It is a fact, however, that in the presence of severe heart disease, cardiac failure and death may be precipitated by a pressor episode brought on either by violent exertion or by the excitement, rage, fear or pain attending the receipt of injury to any part of the body (Moritz, 1954).

That severe heart disease is often compatible with an apparent state of health is well known.

Moritz and Zamcheck (1946) found this true in a study of causes of unexpected death of young soldiers (17 to 37 years old) during World War II. Although these soldiers had recently passed one or more complete physical examinations in which neither a real nor a potential threat to health was recognized, postmortem examinations disclosed various forms of advanced heart disease of which occlusive coronary atherosclerosis comprised the largest number. The increased frequency with which the onset of the fatal attack of coronary insufficiency occurred during periods of strenuous physical exertion lends support to the opinion that a pressor episode, whatever its cause may be, is potentially dangerous to an individual whose coronary arteries are too narrow to permit an increased flow of blood through them.

This observation is not in disagreement with Master and associates (1937) who rightfully contend that coronary thrombosis is rarely the result of trauma or exertion.

In those soldiers dead of a postexertional attack of acute coronary insufficiency, in whom thrombosis was found, it was apparent in all instances that the thrombus had begun to

form before, and not after, the episode that precipitated the fatal collapse. The only circumstance known to the author in which it appears that a pressor episode may be instrumental in precipitating coronary thrombosis is in relation to the kind of thrombosis that results from the rupture of a subintimal hematoma. Spontaneous hemorrhage from capillaries at the base and sides of a coronary atheroma leading to the formation of an expanding subendothelial hematoma which encroaches upon and obstructs the lumen is an occasional cause of acute coronary insufficiency. On several occasions the author has investigated deaths in which it appeared that bleeding into a coronary atheroma had been precipitated by an acute pressor episode and that intraluminal thrombosis had occurred at the site where the hematoma had ruptured through the intimal endothelium.

Another indirect relationship between trauma and heart failure is that represented by the development of acute myocardial anoxia during a period of posttraumatic circulatory failure. Certainly an important factor in determining the outcome of posttraumatic or surgical shock is the systemic anoxia that develops incident to peripheral circulatory failure. In the presence of atherosclerosis, some parts of the body may suffer more than others during the period of circulatory failure. An occasional complication of, or sequel to, shock in a person suffering from atherosclerotic heart disease is the development of nonthrombotic myocardial infarction. Thus, disability or death from myocardial insufficiency may result from posttraumatic shock.

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Neoplasms of the Pericardium and Heart

OTTO SAPHIR

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Introduction. Primary tumors of the heart are rare. Mahaim (1945) made a careful search of the available literature, and found 413 primary tumors of the pericardium and heart. Of the 132 tumors which he regarded as malignant, 45 arose from the pericardium and 87 from the myocardium. It must be realized, however, that among the reports which he included from the older literature, several are open to question. In view of the apparent rarity of these tumors, it is remarkable that a few actually had been diagnosed correctly some time before the death of the patient. By the use of modern methods of tracing the arterial tree, and of catheterization of the cardiac chambers, it may be possible eventu-

ally not only to diagnose but actually to locate primary cardiac tumors more precisely, prior to consideration of their surgical removal. The following discussion is designed not only to give a classification, an anatomic description and a review of pertinent cases, but also to present such facts as may be important for the clinical recognition of primary cardiac tumors. For practical purposes, certain lesions will be included here which in the strict sense of the word are not true tumors, such as cysts, leukemic infiltrations and Hodgkin's disease.

Classification. Tumors of the heart are usually classified as found principally in the pericardium, endo . . . or myocardium.

Such a classification does not imply that the tumors actually arise from these structures, since certain myocardial tumors are believed to arise from misplaced pericardial (meso-

thelial) structures. In the following discussion, as far as feasible, this classification will be employed.

PRIMARY TUMORS OF THE PERICARDIUM

Tumors arising from the pericardium are rarer than those originating within the myocardium. Mahaim was able to collect 84 tumors of the pericardium (Table XIII-1), the majority of which were malignant; 24 were mesotheliomas (coelotheliomas) and 20, sarcomas.

TABLE XIII-1

Frequency of Various Pericardial Tumors,
According to Mahaim (1945)

Fibromas	7
Lipomas	3
Angiomas	10
Coelotheliomas (malignant mesotheliomas)	24
Sarcomas	20
Miscellaneous, cysts	19
Unclassified, malignant	1

Mesothelioma

Mesotheliomas, arising from any serous membrane, are very rare, and a few authors deny their existence. Yet, on rare occasions, every pathologist who has extensive autopsy material at his disposal encounters a tumor which obviously has arisen from a serous membrane. Microscopically, such a tumor may consist of large cells, cuboidal in shape, with eccentrically placed nuclei. Sometimes these cells form pseudoglandular structures, and closely resemble those swollen mesothelial cells so often encountered in chronic inflammation of serous membranes. If a carefully conducted postmortem examination excludes a primary tumor elsewhere, one is justified in designating the tumor of the serous membrane as a primary mesothelioma or, according to the French and also the German literature, a coelothelioma.

Dawe and co-workers (1953) reviewed the literature and reported a diffuse fibrous mesothelioma of the pericardium in a 25-year-old man. Sarrell (1955) reported a primary meso-

thelioma which had metastasized to one of the hilar lymph nodes of the lungs.

Bergman and Jacobson (1958) reported a mesothelioma of the pericardium which was associated with extensive involvement of the pleura, so that primary origin from the pericardium could not be definitely established. The neoplasm invaded the myocardium, extended to the endocardium, and gave rise to widespread metastasis.

Thomas and Phyllion (1957) observed a mixed type of primary mesothelioma of the pericardium in a 78-year-old Negro. Death was caused by hemorrhage into the pericardial cavity. The neoplasm was composed of fibrous elements and epithelial-like structures arranged in parallel rows. Kubat and Todorovičová (1956) reported a



Figure XIII-1. Tumor of pericardium termed endothelioma, but obviously a mesothelioma. The epicardium is exposed. Note nodules on both visceral and parietal surfaces. (From Dick, J. C.: *Endothelioma of the pericardium*. *J. Path. and Bact.*, 47:43-46, 1938. Figures XIII-1, 2 and 3 are reproduced by courtesy of the publishers.)

primary malignant mesothelioma of the pericardium in a 61-year-old woman.

Description. The case report of a malignant mesothelioma by Reals and associates (1947) contains a characteristic description. This tumor was found in a 58-year-old white man. The pericardial sac was tense, distended, enlarged, dark blue and contained 1000 ml. of bloody fluid. The heart weighed 450 grams. The surface of the left ventricle and the entire conus of the heart were studded with hard white masses measuring up to 3 cm. in diameter. The right ventricular surface was almost completely covered with coalescent masses which invaded the heart muscle for a depth of 0.5 cm. Extending from the pericardial cavity along the surface of the pulmonary artery were many small nodules 1 to 3 cm. in diameter. The bronchi were carefully dissected, but no tumor could be found. Metastatic growths were present in the hilar nodes, right pleura, right lung and both kidneys. Microscopically, the neoplasm was highly cellular and pleomorphic. The cells grew in cords with a slight suggestion of whorling, but no definite alveolar arrangement was seen. The nuclei were large with prominent nucleoli, the cytoplasm was acidophilic and finely granular, and mitotic figures were numerous.

Diagnosis. In the absence of more reliable criteria, the diagnosis of pericardial mesothelioma must rest to a great extent on a process of elimination. Robertson (1924) reported a neoplasm originally diagnosed as a primary pericardial tumor but subsequently proved to be metastatic from a primary bronchogenic carcinoma. Willis (1938) concluded that mesotheliomas of serous membranes do not have distinctive histologic criteria. In order to render a diagnosis of "mesothelioma," it is necessary to perform a complete postmortem examination and exclude every epithelial structure in the body as a possible source of carcinoma. In regard to histologic findings, Dick (1938) remarked that, in his tumor (Figure XIII-1), the elongated acini lined by flattened cells did not resemble primitive vascular channels sufficiently to permit classifying the tumor as a lymphangioendothelioma. He asserted that there was a resemblance to the enlarged lymphatics sometimes seen in inflammatory conditions. The likeness of the cellular lining of the more regular acini to the groups of young proliferating pericardial cells (Figures XIII-2 and XIII-3) found in organizing pericarditis strongly suggested a close genetic relationship. This viewpoint was also supported by the irregular alveolar

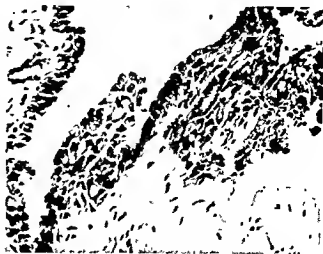


Figure XIII-2. Photomicrograph of tumor shown in Figure XIII-1. Note tumor cells lining connective tissue stroma. X 350.

arrangement, the variation in size of the acini, and the findings of large irregular intercommunicating channels.

Sarcoma

Steuer and Higley (1935) divided pericardial sarcomas into those limited to the pericardium and those which invade the myocardium.

In their case of sarcoma limited to the pericardium, a large mass within the pericardial sac grossly had the contour of the heart, measured 25 by 19 by 13 cm., was nodular, rubbery in consistency, and together with the heart weighed 2450 grams. On section, the heart was entirely surrounded by neoplastic tissue which extended from the epicardium outward, obliterating the

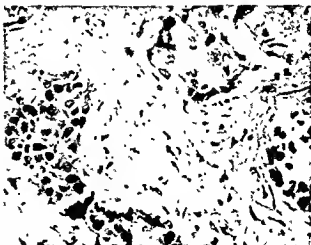


Figure XIII-3. Tumor cells similar to those shown in Figure XIII-2, invading the subpericardial connective tissue. Hematoxylin and eosin. X 350.



Figure XIII-4. Angioma of epicardium (WCGH, 46 A 143)

pericardial sac and being intimately attached to the pericardium. The tumor was made up of multiple gray soft nodules which involved the epicardium and compressed the myocardium from without but did not invade it; it also surrounded the pulmonary trunk and ascending thoracic aorta. On microscopic section, the tumor consisted for the greater part of moderately sized discrete cells with an oval nucleus and a scant rim of acidophilic cytoplasm. The stroma consisted of short, thin, acidophilic fibers which tended to form a reticulated architecture.

Parker and associates (1940) recorded a primary sarcoma of the pericardium which involved the myocardium. A large mass filled the middle portion of the mediastinum and a large part of the left side of the thorax and compressed the left lung. The mass appeared to be enclosed within a distended sac and was firm and solid, except for a portion near the base of the heart which was fluctuant. On cross-section it was seen that a yellow-white mass completely encased the heart and distended the pericardial sac. In some regions the neoplastic tissue was firm, in other regions soft and encephaloid. Large and small areas of hemorrhage and firm white bands of fibrous connective tissue extended through the tumor. Although the tumor as a whole seemed rather sharply demarcated from the heart muscle, it had invaded the myocardium in some areas.

Bowman (1938) described a primary sarcoma of the pericardium which produced metastases to the lymph nodes in the region of the aorta. A myxofibrosarcoma of the pericardium with compression of both atria and of the right ventricle was reported by Schmidt (1948). He believes that this tumor arose on the basis of a faulty development of the primitive mesenchyma.

Teratoma

An intrapericardial cystic teratoma, reported by Beck (1942), showed squamous epithelium, sebaceous glands, sweat gland and hair follicles, endometrium, epithelium resembling that of the upper and lower gastrointestinal tract, smooth muscle, fat and lymph follicles. The tumor was recognized clinically and was successfully removed at operation.

Claireaux (1951) and Basora-Defillo and Lichtenberg (1956) likewise described pericardial teratomas. The latter found only 8 such instances on record.

Leiomyoma

A leiomyoma of the pericardium was reported by Brandes and associates (1942) in a 19-year-old male.

They found a mass bulging from the pericardium over the left atrium and base anteriorly when incised, it allowed the escape of about 60 ml. of bloody fluid. Microscopic examination of the tumor revealed uniformly appearing elongated cells with long slender nuclei, most of which had blunt ends, and with pale-staining but definitely acidophilic cytoplasm. Hemorrhages were present in some areas. Death was unexpected and was probably caused by compression of the atrium by the tumor, the compression having been suddenly increased by hemorrhage. The authors believe that this is the second case of this type on record.

Hemangioma

Angiomas are very rare (Figure XIII-4). Lymphangiomas (Halonen *et al.*, 1955) and hemangiomas (Reiner and Silberg, 1953) have been reported. Most of these lesions are now classified as hamartomas. In fact, Fisher and associates (1951) reported a tumor which they actually termed hamartoma of the lymphatic type (lymphangioma).

Pericardial Cysts

Pericardial cysts or coelomic cysts are lined by mesothelial cells which, in some instances, are difficult to distinguish from vascular endothelial lining cells. Lambert (1940) thought that such cysts may be caused by failure of

primitive mesenchymal lacunae, which form the pericardium, to fuse with each other. For a discussion of other cysts, see Cysts of the Myocardium. A large pericardial cyst, designated as a coelomic cyst, was reported by Gerbasi (1954).

TUMORS OF ENDOCARDIUM AND MYOCARDIUM

Incidence. The variation in incidence of primary cardiac tumors as encountered at autopsy may be seen from Table XIII-2.

Table XIII-3 lists various types of tumors reported.

Age. Cardiac tumors occur at all ages. In Mahaim's series, the ages of persons with myxoma of the heart varied from birth after 8 months' gestation to 79 years. There were 5 instances in the first decade, 5 in the second, 14 in the third, 12 in the fourth, 16 in the fifth, 13 in the sixth, 8 in the seventh, and 3 in the eighth decade.

Sex and Race. There is no appreciable difference in the incidence of cardiac tumors between the sexes. Since most of the perti-

nent literature originated in European countries, no statement can be made in regard to the incidence of these tumors among various races. Isolated reports are available of such tumors in the Negro race and in members of the Mongolian race. Cardiac tumors are also found in the animal kingdom, and further reference to such occurrence will be made subsequently.

Clinical Features. A few instances of cardiac tumor diagnosed during life have been reported. Mahaim stated that of all case reports on cardiac tumors, the correct clinical diagnosis was made 23 times and was suspected in 5 other patients. However, only 8 of these 23 patients disclosed a tumor that

TABLE XIII-2
Incidence of Primary Cardiac Tumors at Autopsy

Author	Year of Report	Number of Primary Cardiac Tumors	Number of Autopsies	Remarks
Thotet	1907	0	3,000	
Bryant	1907	1	2,942	A rhabdomyoma.
Karrenstein	1908	0	6,655	
Morris	1933	1	9,000	A round cell sarcoma.
Lymburner	1934	4	8,550	
Shelburne	1935	3	12,000	
Polha and Gogol	1930	154	36,000	Based on all reports in literature up to 1936; these authors believed this incidence to be too high.
Benjamin	1939	12	40,000	
Scott and Garvin	1939	0	11,000	
Ravid and Sachs	1943	1	1,888	
Straus and Merliss	1945	0	30,000	
		3	1,550	
Leach	1947	1	648	Autopsies performed on viable fetuses; a tumor, a rhabdomyoma, was found in a stillborn fetus of 6½ months.
		1	6,274	Total included 509 autopsies on viable fetuses and newborn infants; a tumor, a rhabdomyosarcoma, was encountered in a boy of 14 years.
Saphir		2	7,869	Sarcoma reported by Perlstein (1918); myxoma, by Strouse (1938).

TABLE XIII-3

Tumors Arising from the Heart (Mahaim, 1945)

Designation of Tumor	Polypoid Tumors	Non-polypoid Tumors	Total
Myxoma	82	23	105
Fibroma	8	29	37
Lipoma	4	10	14
Angioma	4	9	13
Rhabdomyoma	—	60	60
Mesothelioma arising in region of Tawara's node	—	5	5
Miscellaneous (cysts and other benign tumors)	—	8	8
Sarcoma	21	66	87
Totals	119	210	329

was primary in the heart. Woll and Vickery (1947) found 2 additional metastatic tumors correctly diagnosed by Hsiung and associates (1940).

Yater (1931), in his discussion of signs and symptoms of primary heart tumors, stressed the following aspects of diagnosis:

A. Clinical types not suggestive of tumor of the heart:

1. Absence of symptoms referable to heart
2. Symptoms of cardiac embarrassment terminally
3. Symptoms of congestive heart failure
4. Sudden death
5. Symptoms suggestive of subacute bacterial endocarditis

B. Clinical types suggestive of tumor of the heart:

1. Heart block
2. Symptoms other than heart block, referable to location of tumor
3. Symptoms of cardiac dysfunction developing without apparent cause in a patient with a known malignant process
4. Accumulations of hemorrhagic, pericardial and pleural fluid
5. Suggestive roentgenographic observations

Woll and Vickery remarked that the following findings were suggestive or diagnostic of heart tumor:

1. Unexplained and intractable cardiac failure, which is often the first and final attack
2. Unexplained and sometimes inconstant

changes in cardiac rhythm, sounds and size, as judged by physical, roentgenographic and electrocardiographic examinations

3. Development of hemorrhagic pericardial effusion. (The presence of neoplastic cells in the fluid may confirm the diagnosis.)
4. Unexpected signs of obstruction of the cardiac blood flow or of the blood flow of the major thoracic vessels
5. A specimen removed in arterial embolectomy which is shown on microscopic examination to be derived from a tumor of the heart

Respiratory difficulty is a striking feature in patients with atrial tumors. Field and associates (1945) remarked that the most characteristic feature of such tumors is the inability to ascribe a satisfactory etiologic cause for the obvious signs of organic heart disease. It is only by careful observation, frequent clinical examinations and accurate follow-up of patients, with this condition in mind, that more definite criteria for early diagnosis may be assembled. There is general agreement that cardiac tumors would be recognized more often if the clinician considered them in the differential diagnosis of a relevant cardiac condition.

Beck (1942) reported a remarkable case in which a cardiac tumor (a cyst), not only was diagnosed clinically, but was successfully removed and the patient lived, even though most of the "tumor" prior to operation had been embedded in the myocardium. The electrocardiographic changes present before operation eventually disappeared entirely and the patient appeared to be cured. The "tumor" proved to be, not a true neoplasm, but a cyst that had calcified walls and contained material having the consistency of packed clay. This was apparently the first time that a benign cyst or tumor of the heart was recognized clinically and removed successfully.

Myxoma

Nature of Lesion. Endocardial tumors are recorded more frequently than all other primary heart tumors. They arise in the region either of the mural or of the valvular endocardium. Depending upon the point of view of the observer, they are classified as true tumors or pseudo-tumors. In the older litera-

ture (see Thorel, 1907), these lesions were almost invariably classified as true tumors. Thorel, however, stressed that not a single instance reported up to that time could possibly be classified as a true unquestionable myxoma but must, in the final analysis, be regarded as an organized thrombus. Husten (1923) also studied critically all the available relevant instances and interpreted the so-called myxomas of the heart as thrombi in various stages of organization. In Husten's series of 86 myxomas, the left atrium was involved 71 times, the right atrium 9 times, the right ventricle 3 times, and the left ventricle 3 times. Within the left atrium the tumor arose from the region of the foramen ovale in 45 instances; the pulmonary veins and the left auricular appendage were the other preferred sites of origin. Seventeen of the 71 instances of tumors in the left atrium did not disclose sufficient data to make them adaptable to analysis. Husten classified these lesions as (1) thrombi, (2) those in which the diagnosis was difficult, being either thrombi or myxomas, and (3) those which fulfilled certain criteria of myxomas. In studying the location of these lesions within the left atrium, he noted that each lesion involved the three regions of the left atrium just mentioned (fossa ovalis, region of pulmonary veins, auricular appendage) in about equal frequency. He, therefore, concluded that the nature of

these three lesions is also most likely identical, i.e., they represent the end-results of organized thrombi. Husten's point of view was opposed by Ribbert (1915) who stated that often the size of these lesions is much more in favor of their neoplastic nature, as is their lobulated and "villous" appearance. Fabris (1923) listed the distinguishing points between thrombi and myxomas, according to Table XIII-4.

Mahaim (1945) pointed out that myxomas often contain blood vessels and may, therefore, disclose hemorrhages and hemosiderin, that fibrin may be found on their free surfaces; and that the microscopic aspects may not aid in the differential diagnosis. He stated that a number of pathologists, after having studied the evidence for and against the neoplastic origin of these structures, admitted their inability to distinguish myxomas from the end-stages of certain organized thrombi. In certain publications, therefore, the histologic diagnosis is left open. Yet, from his personal experience, Mahaim concluded that localized proliferations of mucous tissue exist within the endocardium which merit the classification of myxoma. An organized thrombus may, as a result of regressive changes, simulate a myxoma. On the other hand, trauma may be responsible for hemorrhage within a myxoma. Mahaim collected from the literature reports of 105 myxomas, of

TABLE XIII-4
Distinguishing Features in Diagnosis of Myxoma and Organized Thrombi.
(Slightly Modified from Fabris, 1923)

Feature	Myxoma	Organized Thrombus
Preferred location	Mitral valve and foramen ovale	Atria
Gross appearance	Thick cauliflowerlike mass	Contour more regular
Surface	Villous, transparent	Granular, opaque
Base	Thin pedicle	
Consistency	Soft, gelatinous	Firm
Endocardial covering	Continuous	At junction of implantation
Cells, number, arrangement and type	Few cells with cytoplasmic processes, in colorless stroma. Cells mainly stellate, isolated or in groups or forming syncytia. Cells embryonic.	Stratified, several layers. External portion composed of granulation tissue with abundant extravasation of red blood cells. Foci of round inflammatory cells.
Special features		
Hemosiderin	Absent	Abundant
Mucin	Present	Absent
Elastic fibers	In vicinity of vessels	Absent
Features in common	Localization in valves, accumulation of bacteria, presence of vessels.	



Figure XIII-5. Intra-atrial tumor reported as myxoma of the left atrium (From Hamilton-Paterson, J. L., and Castleden, L. I. M. Intracardiac tumours, *Brit. Heart J.*, 4:103-114, 1942. Reproduced by courtesy of the publishers.)

which 82 were pedunculated and 23 sessile. One argument often used against the thrombotic origin of myxomas is that the latter are extremely rare in the ventricles. According to Mahaim, only 20 such instances are recorded in the literature. If so-called true myxomas of the atria were organized thrombi, one would expect to find many more such lesions in the ventricles where thrombi are very common. It is, therefore, argued that myxomas and thrombi have nothing in common and represent two different lesions. Mahaim also found that myxomas are encountered much more frequently in the left atrium than in the right. Of the 82 pedunculated myxomas, 68 were in the left atrium and only 14 in the right.

Engle and Glenn (1955) stated that 127 instances of myxomas have been reported, and that this tumor is the most common primary cardiac tumor. Cases of myxomas have been reported by Mills and Plulpott (1951), Blum (1952), Goldberg and associates (1952), Kirkeby and Leren (1952), Cropper and Winstanley (1955), Engle and Glenn (1955), Maronde (1955),

Stephen (1955), and Jackson and Garber (1958).

"Polyp." In the French literature the term "polyp" is often used both in the sense of a pedunculated neoplasm and of a pedunculated thrombus, making it rather difficult for a reviewer to find the exact meaning of "polyp" in a particular instance. Since "polyp" means a pedunculated mass or neoplasm arising from a mucous membrane, the term should never be applied to a cardiac lesion.

Gross Appearance. Yater (1931) described the gross and microscopic appearances of myxomas. They range in size from about 0.4 to 8 cm. in largest diameter. They may be smooth and rounded, lumpy or polypoid and villous, and as a rule, the surface is smooth and glistening, and the appearance, gelatinous (Figure XIII-5). They are usually pale, yellow, blue-gray or yellow-brown, often with hemorrhagic areas on the surface, and sometimes partly covered with fibrin. The consistency is more or less elastic and on cut section, they are gelatinous and often hemorrhagic. They are usually attached by a short stalk and are entirely intracardiac.

Microscopic Features. The tumor is covered with the normal endothelium of the endocardium. The groundwork is an amorphous, finely granular or finely fibrillar material which may or may not stain as mucin. Cells of different varieties are seen, varying in number in different parts of the same mass; often they are relatively few compared to the total amount of myxoma tissue. Many have large stellate cells typical of myxomatous tissue. Some also have cells that are multinucleated, or cells that are fusiform. Inflammatory elements such as lymphocytes and plasma cells are often seen. Blood vessels are usually present, sometimes numerous, but often scanty; they are usually delicate and appear as mere capillaries with endothelial walls. Small hemorrhages and scattered erythrocytes are commonly present, together with pigments consisting of hemosiderin and hematin. Connective tissue fibers and often elastic fibers are found.

Dick and Mullin (1956) reported the presence of fungi within a left atrial myxoma. The literature also contains reports of "malignant" myxomas (Fenster, 1933; Ringertz, 1942). A critical re-

of Ringertz' report suggests the possibility the original lesion was a thrombus which gave rise to multiple emboli, while Fenster's tumor should be classified as either a spindle cell myxoma or, perhaps, a neurogenic sarcoma.

Evaluation of Myxoma. From the foregoing it may be seen how difficult it is to differentiate between myxomas and end-stage organized thrombi. One is certainly justified in questioning the existence of true myxomas of the heart. Prichard (1951) concluded that myxomas form a uniform group of tumors, occurring in a definite location in the heart and having a characteristic gross and microscopic appearance. He reported 2 instances of myxoma and pointed out that the lack of evidence indicates that they are true neoplasms. It seems obvious that a more conservative point of view should be adopted and that any sessile or pedunculated lesion which could perhaps be interpreted as myxoma should be regarded as the end-stage of an organized thrombus unless definitely proved otherwise. One cannot say that such definite proof will be forthcoming. In a study, entitled *Intracardiac Tumors*, Hamilton-Patterson and Castleden (1942) list such a lesion of the left atrium as "pseudomyxoma."

The difficulty of distinguishing between myxoma and organized thrombus may be inferred from Weinstein and Arata's report (1949). They described a neoplastic lesion in the left atrium which they thought had produced mitral stenosis and insufficiency. The tumor was interpreted as a myxoma. The gross picture of the heart, however, shows definite thickening of the chordae tendineae of the mitral valve. Also the presence of an embolus in one of the femoral arteries would indicate that the "myxoma" was probably a thrombus. In the report of Orr (1942), who described a polypoid tumor of the left atrium of the heart, a number of endothelial structures were present microscopically, which led the author to conclude that this was essentially an endothelioma. A picture of the gross specimen is included showing the "tumor" and the mitral valve, and the chordae tendineae are described as thickened and shortened. Thus, it seems that the mitral valve was the seat of an old endocarditis, which throws doubt on the neoplastic nature of this lesion.

Lekisch (1957) reported a so-called primary

myxoma of the left atrium. He was impressed with the histologic findings of fibrosis, cartilage and even calcification at the base of the "tumor." Present also was evidence of old hemorrhage with deposition of much hemosiderin. Between a loose network of elongated spindle-shaped cells there was a matrix of homogeneous, metachromatic material, suggesting the presence of large amounts of mucin. From the microscopic description, this lesion may well be thrombus that was partly degenerated and partly organized.

The preferred location in the left atrium speaks strongly for myxomas being thrombi with secondary changes. Evidence of old mitral endocarditis should always be interpreted as favoring the formation of atrial thrombi. Blum (1953) demonstrated myxomatous transformations of out-spoken organized thrombi. While he attributed this to cellular proliferation combined with permeation of edema fluid, he also believed in the existence of true myxomas.

Clinical Significance. So-called myxomas are often incidental autopsy findings, unsuspected clinically. Yater (1931) remarked that many of the myxomas are interesting because of their size, structure and pedunculated nature, which allows them to plug an orifice of the heart, usually the mitral. Straus and Merz (1945) stated that a large tumor of an atrium with a ball-valve action on either the mitral or the tricuspid ring, producing murmurs that are affected by a shift in the position of the body, should certainly be susceptible to clinical diagnosis; and yet, in no case of benign tumor of this type had the diagnosis been made before death. Unexpected death may apparently result from sudden occlusion of either the mitral or the tricuspid orifice by an intracavitary pedunculated tumor (Yater).

Beck (1942) and Coulter (1950) stated that it seemed that some of the soft myxomas arising from the endocardium could be surgically removed; in 1956 Scannell and associates reported the removal of such a tumor.

Myxomas of Heart Valves. Myxomas arising from the heart valves are also the subject of much controversy. Ribbert (1924) pointed out that myxomas of the valves are almost invariably larger than thrombi, and it seems difficult to believe that complete organization of thrombi could materialize from the valvular



Figure XIII-6 Lipoma of left ventricle, ventral view. Heart and tumor weighed 530 Gm. (Courtesy of Dr. Richard E. Olsen.) (WCGH, 58 P 232)

lar endocardium. Organization of a large thrombus usually results in its encapsulation with regeneration of the endocardial cells, the center of the thrombus still being liquid or becoming liquefied secondarily. However, it does not seem likely that the center of a large thrombus may ever be completely replaced by fibrous tissue with secondary myxomatous degeneration, so as to simulate a myxoma with diffuse myxomatous tissue. Ribbert also remarked that an organized thrombus would eventually lead to scar tissue within the adjacent valvular tissue, as seen in healed thrombo-endocarditis.

Three types of so-called occlusive myxomas ("polyps") of the mitral valve are recognized by Mahaim (1945):

1. Occlusive pure mitral "polyps" with clinical signs of stenosis of mitral orifice and without mitral lesions at autopsy
2. Occlusive pure mitral "polyps" without signs of stenosis of mitral orifice, with or without systolic murmurs of functional mitral insufficiency
3. Occlusive mixed mitral "polyps" with associated mitral lesions. Clinical signs of stenosis of mitral orifice are constant but often masked by severe arrhythmia

Jaleski's (1934) report of a so-called myxoma of the tricuspid valve is interesting insofar as justifiable criticism may be presented in regard to the classification of this lesion. His patient was

a 62-year-old colored woman who suddenly collapsed 5 days after extraction of a cataract and died the next day. On the middle portion of the anterior leaflet of the tricuspid valve was a small spherical papillary mass, projecting above the surface of the valve to which it was attached by a wide pedicle. Its surface was finely nodular and it had a translucent gelatinous appearance. Stained with hematoxylin and eosin, the mass was entirely lined by endothelium, its matrix was pink and contained only a few cells, but no blood vessels were present; the pedicle, on the other hand, contained many stellate and spindle-shaped cells which had fine processes extending from them into the fine fibrillar groundwork present throughout the lesion. Thus the gross and microscopic description of this pertinent lesion, reported as myxoma of the heart valve, would suggest that this is a true tumor of the heart. However, a gross picture of the right ventricle, included to show the tumor, also shows evidence of old endocarditis, which immediately raises doubt as to the neoplastic nature of the lesion.

Other Terms for Myxoma. In this connection it may be mentioned that Warthin (1916) thought that some of the so-called myxomas of the heart represented gummata, and for these he coined the term "myxogummata." Some of the more recent reports of these small valvular lesions also cast doubt as to their true nature. Thus, Engel (1932) spoke of a "peculiar fibromyxomatous hyperplasia" of the mitral valve. He regarded this lesion as a transition between hyperplasia and tumor.

"Fetal Endocarditis." In reviewing a number of reports of myxoma of the heart, one is reminded of the small myxomatous lesions which are encountered not rarely on various valves of stillborn or newborn infants, which in the older literature were called "fetal endocarditis." Gross (1911) has shown that these structures are remnants of the jelly-like material which makes up the original endocardial cushions. It is conceivable that such structures may persist and eventually become organized, giving rise to either so-called valvular myxomas or fibromas.

Excrecences of Lambl. Lambl in 1856 described small villous, comb- or tassel-shaped excrecences situated principally on the free borders of the valves and rarely involving the cusps on the line of closure. Kirch (1927)



Figure XIII-7. Lipoma of ventral wall of opened left ventricle of heart shown in Figure XIII-6.

stated that Lambl's excrescences are definitely not tumors but, according to Ribbert (1924), are the result either of organization of thrombi or of proliferation of the subendocardial connective tissue. Kirsh noted Lambl's excrescences often close to the corpus arantii. Gunzel (1933) asserted that Lambl's excrescences of the aortic valve are much more common than is usually assumed. He maintained that with increasing age they are more frequent. They are not the result of organizing thrombi and they do not constitute products of inflammation, since they are always avascular and free from cellular infiltration. He believed that because of the continuous, perhaps abnormal, systolic and diastolic pressure,

a tear of the lining endocardium may cause the previously stretched and broken collagenous or elastic fibers to project over the endocardial surface. Eventually these fibers become endothelialized again.

Magarey (1949) examined the mitral valve in 280 autopsies. He found Lambl's excrescences in 85 per cent and determined that their incidence increased with age. He believed that they are a manifestation of wear-and-tear and part of the normal aging process of the valve. They are the result of organization of partially attached fibrin on the surface of the valve. This process occurs repeatedly and leads to gradual thickening of the cusps.

OTHER TUMORS OF HEART

Fibroma. Fibromas of the heart arise from the subendothelial connective tissue of endocardium (Figure XIII-8). Almost all the reported fibromas are located on heart valves. Mahaim (1945), collected many reports of fibromas of the various valves. It was sometimes difficult to decide from the literature whether the lesion in question was a fibroma, myxofibroma, myxoma, fibrohemangioma, or an excrescence of Lambl. Such lesions were

found on the mitral valve 3 times, on the aortic valve 8 times, on the pulmonic valve 7 times, and on the tricuspid valve twice.

Kulka (1949) reported an intramural fibroma in the left ventricle of an 8-month-old infant who had died unexpectedly. McCue and associates (1955) encountered a myocardial fibroma in a 4-year-old child who also had subaortic stenosis. Haviar and associates (1956) reported a fibro-



Figure XIII-8 Pedunculated fibroma. X 175. (Courtesy of Armed Forces Institute of Pathology, Acc 38,558.)

lipoleiomyoma. Its presence was recognized clinically and it was surgically removed.

A papillary branching fibroma of the tricuspid valve was reported by Branch (1931). The tumor consisted of papillary stalks which were composed of a single or compound core of dense collagenous fibrils surrounded by loose connective tissue, outside of which was a layer of homogeneous material covered by endothelium. The tumor contained no blood vessels. Hertzog (1936) also described a fibroma of the middle cusp of the aortic valve. He stated that there was no evidence of old endocarditis. Hertzog remarked that his tumor was similar histologically to some of the reported cases of myxoma of the heart valves. However, myxomatous tissue could not be demonstrated.

Roth and Spain (1952) described a tumor which they believed to be a primary granular cell myoblastoma of the left atrium. It was firm, covered by pericardium and fixed to the subepi-

cardial tissue and myocardium. The cells were fairly uniform in size and shape, infiltrated the interstitial tissue, and contained an abundant cytoplasm which appeared to be granular or clumped.

Tumorlike structures, consisting of fibrous and elastic tissues, may occur on a valve. These are regarded as hamartomas, and have been called fibro-elastic hamartomas (Dudley et al., 1956). In Raeburn's case (1953) the lesion was papillary.

Other rare lesions which resemble fibromas may also be regarded as hamartomas. These are encountered principally in children and consist microscopically of collagen with fibroblasts, surrounded by cardiac muscle, and may contain blood vessels, fat and nerves. Bigelow and associates (1954) believed that this tumor is most likely derived from primitive cardiac mesenchyme and suggested the term "fibroma of primitive type" or perhaps "fibromyoma," implying that

the muscle fibers in these tumors are not "trapped" fibers but constituents of the tumor. An apparently similar tumor, for which the term "undifferentiated mesenchymal tumor" was suggested, was described by Conlon (1956).

Lipoma. Lipomas of the heart (Figures XIII-6 and 7) are extremely rare. Mahaim (1945) recorded 14 such tumors.

A typical lipoma of the heart was encountered by me in the right atrium of a 50-year-old woman who died suddenly. The tumor was bright yellow, measured 3 cm. in greatest diameters, was covered by epicardium and bulged into the right atrium. It seemed to be well circumscribed grossly, but microscopically was not circumscribed and had no evidence of a capsule, a few atrophic muscle fibers were scattered throughout the tumor. It was apparent that the fatty tissue had infiltrated the myocardium, replacing the muscle fibers. The same changes are found in fatty infiltration of the myocardium (Saphir and Corrigan, 1933), in which the subepicardial fatty tissue also extends into the adjacent myocardium, produces atrophy of the fibers and, like a malignant tumor, eventually replaces the muscle fibers. Thus, the question must be raised whether these lipomas of the heart represent circumscribed areas of fatty infiltration or are true benign tumors which grow by expansion and are not surrounded by a capsule.

Shea and Muehsam (1952) stated that only 21 lipomas have been reported. They found a lipoma arising in the wall of the right atrium. Apparently, the atria are much more frequently involved than the ventricles.

Angioma. Mahaim asserted that pure angiomas of the heart are very rare, only 13 such tumors having come to his attention. They should be clearly distinguished from varicose dilatations (see page 877) and they may be associated with proliferation of endothelial lining cells.

A small tumor of this type was found by Schuster (1914) in a newborn infant on one of the papillary muscles of the right ventricle close to the attachment of a chorda tendinea. This nodule measured 2.5 by 1.5 cm. in greatest dimensions. Microscopically, it consisted of two parts; one part was interpreted as representing the end-result of a circumscribed inflammation of the endocardium, and the other part, as a true tumor, a cavernous hemangioma. The author denied the

existence of any relation between the circumscribed inflammation (*endocarditis*) and the tumor. This report raises the question as to whether the structure described as cavernous hemangioma is identical with a so-called blood cyst found on the heart valves in the newborn (see page 885).

Angio-Reticuloma. Angiomas should not be confused with true benign tumors of the angio-reticuloma type of the endocardium which Mahaim (1945) believes are similar to those occurring in the cerebellum and spinal cord, as described by Cushing and Bailey (1928).

Nicod (1945) described, in a woman of 74, a tumor of the endocardium located in the left atrium near the foramen ovale. Microscopically, it showed angiomatous and reticuloendotheliomatous structures. Mahaim speculated on the possible changes which might occur in such a tumor developing in a young person, if it was subjected for a long time to the trauma of the blood stream and of cardiac contraction. He believed that changes might occur in such a tumor which would simulate the appearances of both a thrombus and a myxoma. He directed attention to the so-called angio-reticuloma of Nicod (1945) and asserted that many of the polypous tumors of the atrium, whose origin at the present time is under dispute, could perhaps be traced to these angio-reticulomas.

Malignant Hemangioendothelioma. A primary malignant hemangioendothelioma of the heart with multiple metastatic nodules in the liver and esophagus was described by Hewer and Kemp (1936).

Gross and Englehart (1937) described another primary hemangioendothelioma of the heart. This diffusely infiltrated the wall of the left atrium and had grown into thrombi which were adherent to the left atrial wall, the mitral valve and the left ventricular wall. There was no evidence of tumor embolism or metastasis outside the heart.

Glassy and Massey (1950) reported a primary hemangioendothelial sarcoma which had involved the pericardium and endocardium. They believed their tumor to be the 349th recorded primary cardiac neoplasm.

Hethrington and Blanchard (1952) reported 2 such tumors which arose in the wall of the right ventricle, penetrated the endocardium and

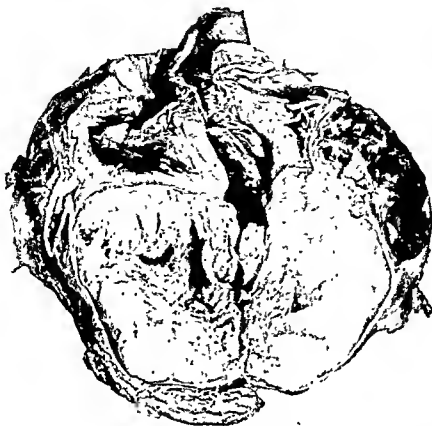


Figure XIII-9. Sarcoma of heart. (Courtesy of Armed Forces Institute of Pathology, Acc 100,969, Neg. 77,204)

spread diffusely over the visceral pericardium. Metastatic tumors were found in the lungs, liver and bone. Brandenburg and Edwards (1954), in a report of this tumor, gave a brief review of the literature and discussed the clinical features.

Stout (1943) contended that a tumor should be regarded as a hemangioendothelioma only if it contained, first, atypical endothelial cells to excess of the number required to line the vessels with a simple endothelial membrane and, secondly, vascular tubes with a delicate framework of reticulin fibers and a pronounced tendency of their lumina to anastomose.

It is open to question whether some of these tumors can be classified under the term *Kaposi's tumor* (sarcoma idiopathicum hemorrhagicum) in which there are multiple vascular foci of tumor formation. Rabson (1938) suggested that hemangioendothelioma and Kaposi's disease may have certain elements in common. Although Ewing (1940) does not mention the heart specifically, he stated that

in Kaposi's disease every organ of the body has been found involved at autopsy.

Rhabdomyoma is described under the term Nodular Glycogenic Degeneration (page 512). From the evidence at hand, it seems that true rhabdomyomas (true neoplasms) of the heart, if they exist at all, are extremely rare. Most, if not all, of the reported instances are examples of localized glycogen-storage disease with or without simultaneous presence of various hamartomas, as in the grain.

Sarcoma of the Myocardium

Malignant primary tumors of the myocardium are very rare.

Perlstein (1918) who reviewed this subject, found only 30 tumors which he regarded as sarcomas, and added one. Mahaim (1945) accepted 87 tumors as true sarcomas but a critical review of these disclosed that apparently not all are primary. Thus Guttman's (1889) so-called primary melanoma is obviously a secondary tumor, the primary tumor very likely having been in the

right eye which had been removed. Leach (1947) and Woll and Vickery (1947) each reported an instance.

The literature of primary malignant tumors was also reviewed by Whorton (1949) who collected approximately 100 cases of primary malignant tumors of the heart. He reported a primary reticulum cell sarcoma, 16 similar instances of which had been observed previously. Engle and Glenn (1955) stated that 125 instances of various primary sarcomas of the heart have been reported, and that myxomas are somewhat more frequent than sarcomas.

The following types of primary sarcomas have been reported: fibrosarcoma, leiomyosarcoma, myxosarcoma, angiosarcoma, reticulum cell sarcoma, rhabdomyosarcoma, and round, spindle, and mixed cell sarcomas. Also primary lymphosarcomas are supposedly found in the myocardium. Yater stated that the majority of sarcomas of the heart arise from the atria, particularly the right atrium, from the inter-atrial septum, and from the pericardium. Mahaim also found the right atrium to be frequently involved. Bryant (1907) found a primary sarcoma in the heart of a dog.

Round and Spindle Cell Sarcoma. Perhaps the most common sarcomas are described as round and spindle cell sarcomas (Figures XIII-9, 10 and 11). Mahaim found 18 round cell sarcomas in the literature, 17 spindle cell sarcomas and 11 polymorphous cell sarcomas.

Hamilton-Paterson and Castleden (1942) described a round cell sarcoma in a heart weighing 600 grams. The entire right atrium was filled with large nodules, all arising from the atrial wall. The tumor was soft and white, with areas of hemorrhage, and one tumor nodule had grown through the inter-atrial septum and projected as a red mass into the left atrium. Microscopically, the cells were large and round with scanty eosinophilic cytoplasm; in one or two areas very large cells had giant nuclei, but no true giant cells were seen. There were no metastatic nodules. A typical spindle cell sarcoma, reported by Holer (1937), was encountered in the right atrium of a 26-year-old woman, and had produced metastatic growths to the lungs. A primary sarcoma, situated in the left atrium, was observed by Adamson (1948). It consisted of spindle and giant cells and was associated with metastatic growths in the duodenum, jejunum, ileum and ascending colon.

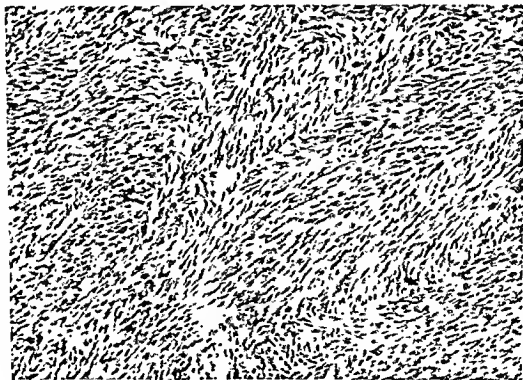


Figure XIII-10. Spindle cell sarcoma. Same case as Figure XIII-9. X 105. (Courtesy of Armed Forces Institute of Pathology, Acc. 100,969, Neg. 77,250.)

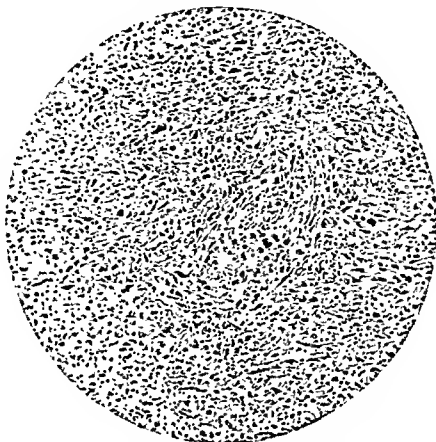


Figure XIII-11. Spindle cell sarcoma of myocardium. It could not be decided whether this was a rhabdomyosarcoma or fibrosarcoma. Hematoxylin and eosin X 100. (WCCB, 45 P 191 W.)

Rhabdomyosarcoma. Rhabdomyosarcomas are rarer than spindle or round cell sarcomas. Mahaim mentioned only 7 instances.

Leach (1947) reported such a tumor in a 14-year-old boy. The heart weighed 350 grams. A bulging mass, slightly paler than the rest of the heart, could be seen about the middle of the anterior wall of the left ventricle. A large yellow polypoid tumor, 5.5 cm. in diameter, growing from the myocardium, filled the cavity of the left ventricle. The base of the tumor involved the anterior wall and the interventricular septum of the left ventricle and extended to the anterior leaflet of the mitral valve, but did not involve it. Microscopically, the striking feature was the presence of areas of ribbonlike bands of cells which branched occasionally and showed longitudinal striations. The cytoplasm was acidophilic and the nuclei were centrally located and oval, with a reticular chromatin network and very small single nucleoli. There were many thin-walled blood vessels. Metastatic growths were found in mediastinal lymph nodes, pleura and intercostal muscle.

Stoll and Lauer (1955) described a rhabdomyosarcoma arising in the left atrium, with metastasis to the lung, pleura, hilar nodes and pericardium. Some of the tumor cells showed outspoken cross-striations. Engle and Glenn (1955) reviewed the literature briefly and described such a tumor in a 4-month-old infant. Manson and Rindskopf (1956) stated their case of rhabdomyosarcoma was the nineteenth one reported. Kahrs (1953) described a rhabdomyolipoma and a rhabdomyosarcoma.

Fibrosarcoma is also rare. Woll and Vickery's (1947) report concerned a 47-year-old woman. The lumen of the mitral valve appeared to be completely occluded by a pale, yellow, firm, slightly lobulated, polypoid tumor, firmly attached by a broad base to the atrial surface of the posterior leaflet and the adjacent atrial wall. The external surface of the tumor was alternately yellow, smooth and firm, and pale pink, granular and friable. On cross-section, the growth fused imperceptibly with the endocardium and formed a coarse, pale gray, homogeneous firm mass with poorly delineated radially arranged bands separat-

ing adjacent peripheral lobulations. Microscopically, the tumor consisted of relatively acellular, irregularly arranged bundles, and whorls of collagenous fibers with connective tissue cells of various sizes and shapes. Most of these cells appeared to be mature fibroblasts, others had plump spindle-shaped vesicular nuclei with abundant granular cytoplasm or delicate extracellular fibrillar projections. Still others were stellate or round with large hyperchromatic nuclei. There were also a few tumor giant cells with amorphous dark nuclei. A solitary metastatic lesion involved a thoracic vertebra. In retrospect, from the description and the accompanying illustration disclosing thick bundles of fibers with palisading nuclei, it seems that this instance, as well as a number of other instances of fibrosarcoma of the heart, might fall into the classification of neurofibrosarcoma.

A primary tumor which took its origin either from the myocardium of the left ventricle or, perhaps, from the pericardium was described by Friedman and associates (1945). In the differential diagnosis, leiomyosarcoma and fibrosarcoma were considered. It is interesting that a single metastatic nodule was found in the myocardium adjacent to the aortic ring. Fibrosarcomas were reported by Roberts and Seal (1951) and, in a 3-month-old infant, by Longino and Meeker (1953).

Fibromyxosarcoma. Very rarely malignant tumors of the heart arise at the root of the pulmonary trunk. Haythorn and associates (1941) described a multiple fibromyxosarcoma arising just above the pulmonary valve, within the pulmonary trunk, attached to the posterior wall about 3 cm. above the corpus arantii of the middle semilunar cusp. These tumors were described grossly as myxomatous "polyps." Their pedicles were united in a common broad base. Microscopically, a striking feature of the "polyp" was the great excess of myxomatous stroma in comparison with the cellular elements. Some of the cells were spindle-shaped with long stellate processes, and others were round or oval. Many of the cells were multinucleated and appeared to be true neoplastic forms. Mitotic figures were numerous in some fields. From the microscopic description, the tumor can perhaps be interpreted as a thrombus undergoing organization and also degeneration. However, a similar tumor was found in the main bronchus on microscopic examination. The occurrence of these lesions also in branches of the pulmonary arteries certainly does not mitigate against the assumption that they are thrombi. The authors paid special attention to a zone of pulmo-

nary arteritis about the pedicle of the tumor which was covered with an organizing thrombus that showed no neoplastic changes. The association of pulmonary arteritis with the base of the tumor suggested to them that the logical sequence in the development of the tumor may have been as follows: pulmonary arteritis with loss of endothelium, "protective" thrombosis, organization of the thrombus with myxomatous metaplasia, sarcomatous change in the myxoma, and secondary extensions to the lungs by way of branches of the pulmonary arteries. The authors thus explain the tumor as occurring on the basis of changes within a thrombus, which to us seems questionable.

A neurogenic sarcoma, histologically resembling a malignant schwannoma, which might have had its origin from the cardiac plexus, was reported by Dammert and co-workers (1955). Courtoy and Potvlieghe (1951) reported a large tumor, arising in the right ventricle, which had destroyed the entire right ventricular myocardium including the terminal portions of the right branch of the bundle of His. This tumor was diagnosed as a reticulum cell sarcoma.

A tumor consisting of foci of typical Anitschkow myocytes was reported by Mainwaring and Ayres (1952). The nuclei contained the characteristic basophilic longitudinal chromatin bar and on cross section, presented an owl-eyed appearance.

Solomon (1951) reported a metastasizing malignant teratoma arising in the right cardiac



Figure XIII-12. Tumor of intra-atrial portion of septum diagnosed lymphangoendothelioma. This tumor should be classified as a mesothelioma arising from the node of Tawara. X7. (From Perry, C. B., and Rogers, H.: Lymphangoendothelioma of the heart causing complete heart block, *J. Path. and Bact.*, 39: 281-284, 1934. Reproduced by courtesy of the publishers.)



Figure XIII-13. Tumor of region of node of Tawara, classified as mesothelioma. Note small pseudoglandular structures lined by cells interpreted as mesothelial cells. (From Mahaim, I.: *Les Tumeurs et les Polypes du Cœur*, Masson et Cie, Paris, 1945. Reproduced by courtesy of the publishers.)

atrium of a 2-year-old girl. A striking feature of the tumor was the histologic resemblance to rare epithelial cysts of the heart and also to mesotheliomas of the pericardium. In view of the relative frequency of mediastinal teratomas, it is assumed that multipotential cells of the mediastinum may have been included within the developing heart and may have given rise to the tumor. For reports of older cases, see Willis (1946).

Polymorphous Cell Sarcoma. A polymorphous cell sarcoma involving the pulmonary artery was described by Martin and associates (1939). It was polypoid, measured 2.5 cm. in diameter, involved the pulmonary valves and the adjacent endocardium, and extended also along the course of the pulmonary trunk to the right and left pulmonary arteries. There were no metastatic tumors.

Sites of Metastasis. Metastasis from primary sarcoma of the heart may be widespread. In Yater's (1931) series of 46 cases, metastatic growths were found in 21. The organs and frequency of their involvement were: lungs, 8 times; lymph nodes, 5 times; pancreas, 4; suprarenals, 3; and liver and kidneys, each twice. In Mahaim's series of 87 cases, the organs and frequency of involvement were: lungs, 24; lymph nodes, 9; liver, 9; kidneys, 8; suprarenals, 7; pancreas, 5, and intestines, 3 times.

Mesothelioma of the Myocardium

A group of tumors of disputed origin occurs

in the region of the atrioventricular node. Today, most of these tumors (Figure XIII-12) are classified as mesotheliomas (coelotheliomas, originating from misplaced epicardial structures).

Apparently the first case of this type was described in 1911 by Armstrong and Monckeberg. The patient was a 5½-year-old boy who had had complete heart block. The tumor was not recognized grossly but only on histologic examination. It was characterized by spaces which were lined by one or two rows of endothelial cells surrounded by dense connective tissue; a number of cords consisting of cells similar to those lining the spaces were also noted (Figure XIII-13). The atrioventricular node was located adjacent to the tumor. This new growth was interpreted as a *lymphangoendothelioma*.

Lloyd in 1929 described an apparently similar tumor in a 39-year-old woman who clinically had had partial heart block. The clinical diagnosis was syphilis of the myocardium but no syphilitic lesions were encountered in either the aorta or heart. There was no gross alteration in the contour of the interventricular septum but, on cross-section of the septum, vaguely outlined clusters of minute cystic spaces, surrounded by a white translucent fibrous stroma, were observed, some of which contained a clear yellow coagulum. On microscopic examination, a definitely neoplastic structure was recognized in the form of cystic spaces lined by several irregular layers of cells, most of which were round or slightly elongated with indefinite cell boundaries. Some of the spaces were separated from each other by a dense fairly cellular connective tissue. In some areas clumps of round or oval tumor cells with vesicular nuclei were arranged in solid cords which, on examination of numerous serial sections, failed to reveal any true tubular structures. A number of the cystic spaces had invaded the region of the atrioventricular node, which contained a few scattered bundles of muscle fibers that were smaller than those of the remainder of the myocardium. Lloyd (1929) and Armstrong and Monckeberg believed that, since the atrioventricular node is especially rich in lymphatics and since the tumors, according to their interpretation, consisted of lymph vessels and proliferated endothelial cells lining these vessels, they should be classified as lymphangoendotheliomas. The localization of the tumor reported by Lloyd readily explains the clinical finding of heart block and, perhaps, the sudden death of his patient.

Grant and Camp (1933) reported a vascular tumor located in the region of the atrioventricular node. This tumor had produced complete heart block and was recognized only on microscopic examination. It was found in the region where the atrioventricular bundle normally bifurcates, and extended through the entire width of the septum, bulging outward at the base of the tricuspid valve to form a small nodule. It consisted of a compact leash of tortuous, irregularly dilated and anastomosing blood vessels, chiefly arterial in structure, and was not sharply limited at its margin. They believed that this tumor should be classified as a rare arterial angioma. However, no detailed description of the vessel walls and their lining cells are given and it would seem likely that this tumor falls into the same classification as those described by Armstrong and Monckeberg, and by Lloyd.

Another apparently similar tumor which had also caused complete heart block was described by Perry and Rogers in 1934. On gross examination, the heart was normal in size and a minute tumor was found just between the interventricular and interatrial septa, bulging slightly into the left ventricle. Microscopically, the tumor closely resembled those described by Armstrong and Monckeberg, and by Lloyd, and was also interpreted as a lymphangioendothelioma. By serial sections, the gradual approach of the tumor to the atrioventricular bundle, its entry at the superior angle of the bundle, and the final complete involvement of the conduction tissue were easily observed.

A detailed description of another similar tumor classified, however, as a primary epithelial tumor, was given by Rezek (1938). This tumor was found in a 71-year-old patient whose electrocardiogram showed a transitory complete heart block. At postmortem examination a diffusely infiltrating carcinoma of the stomach was found with metastasis to the regional lymph nodes. Only on microscopic examination was a tumor found very close to the atrioventricular node. It consisted of a number of channels, lined by one or two layers of cuboidal cells, resembling and interpreted as epithelial cells. The specific muscle fibers in the region of the tumor were atrophic and occasionally disclosed actual necrosis. A moderate amount of scar tissue and foci of calcification, minute areas of hemorrhages, and infiltration of lymphocytes were found close to the tumor. Because of the morphologic appearance of the tumor, malignancy was ruled out. It was

especially emphasized that this tumor could not possibly be interpreted as being metastatic from the primary carcinoma of the stomach. Rezek pointed out a close resemblance between the cystic structures of this tumor and their lining cells, and the glandular structures found in the embryonal intestinal tract. He recalled that, in serial sections of very young embryos, a close local relationship is noted between the cardiac Anlage and the anterior wall of the primitive foregut. He concluded that it is possible that the cystic structures accompanying the tumor may arise from heterotopic epithelium of the foregut, displaced in the heart during an early stage of embryonic development. For this reason, he classified this tumor as epithelial. Because of the histologic similarity of this tumor and those described by Armstrong and Monckeberg, Lloyd, and Perry and Rogers, Rezek concluded that all these tumors are obviously of the same origin. Leicher (1948) concluded that the glandlike structures in his tumor were epithelial in nature. He thought that they were hamartomas arising from misplaced caudal portions of the primitive gut.

Still a different origin for these tumors, which seems to be the most likely one, was advanced by Mahaim (1945). He reported a tumor in the heart of a 24-year-old woman who had had a complete heart block clinically. The tumor was located in the region of the node of Tawara and corresponded in every detail to those just described. Mahaim stated that the tumor was a primary benign multilocular neoplasm and that this type of neoplasm always produces complete or partial heart block by destruction of the atrioventricular node in its posterior portion. However, he emphasized that this tumor is neither a lymphangioendothelioma nor an epithelial tumor, but originates from proliferating embryonal epicardial (mesothelial) cells during the early stage of development of the node. Thus, it should be classified as a *mesothelioma* (*coclothéliome* Tawarien bénin).

A rather unique lesion of the heart, was reported by Dosch (1941). He described a nodular tumor interpreted as an accessory thyroid nodule, within the interventricular septum, bulging beneath the endocardium into the right ventricle just below the pulmonary valve. He did



Figure XIII-14. Metastatic neoplasm of right ventricle from primary adenocarcinoma of stomach

not believe that this structure represented misplaced thyroid tissue but should be interpreted as the end-result of growing dedifferentiated endodermal epithelium. Dosch mentioned that such dystopic thyroid tissue has been described several times in the heart of the dog. He discussed the possibility that certain lymphangio-endotheliomas and mesotheliomas, arising in the interventricular septum, may perhaps also be examples of such accessory thyroid nodules. However, it is well known that occasionally benign-appearing nodular colloid goiters which in reality are malignant tumors (follicular carcinoma), produce metastatic growths (so-called metastasizing colloid goiter). Dosch did not mention examination of the thyroid in his case and thus the question must be raised whether the thyroid structure found in the septum of the heart constitutes a metastatic nodule of a primary so-called metastasizing colloid goiter.

A tumor of the right atrium, consisting of both myxomatous and glandlike or cystic structures of

the type just discussed, was described by Anderson and Dmytryk (1946). Microscopically, most of the tissue had a myxomatous appearance and was composed of relatively few cells within an abundant, loose, pale-staining stroma which was faintly basophilic or eosinophilic. Glandular cystlike spaces lined by cells resembling epithelium were noted in various areas of the tumor. The lining cells varied in shape from flat endothelial type to tall, closely packed, columnar cells with basal nuclei. The authors advanced three possible explanations of the cystlike spaces: (1) They represented lymph vessels; (2) they were derived from heterotopic inclusions of endodermal tissue of the primitive foregut; or (3) they were of pericardial (mesothelial) origin. Anderson and Dmytryk were inclined to believe that the evidence favored a pericardial origin of the epithelioma-like structures, and that mesothelial cells of the visceral pericardium have often been observed to differentiate into tall columnar cells, as encountered in their tumor.

A tumor involving the inferior vena cava, right atrium, right ventricle and the epicardial surfaces of the aorta and pulmonary trunk, was reported by Reisinger and associates (1942). From the description, it is difficult to venture an opinion whether (1) this tumor was primarily located in the wall of the vena cava; (2) the primary tumor was located in the heart; or (3) there were primary lesions in both vena cava and heart. Histologically, irregularly elongated cells were found with large, round or oval nuclei and a scanty cytoplasm which stained faintly eosinophilic. Intermingled with these cells were roughly polygonal or round cells with eccentrically placed bean-shaped nuclei which occupied more than half of the cells. The cytoplasm took a faint neutral stain and contained no granules. There were scattered lymphocytes and polymorphonuclear leukocytes and an occasional eosinophilic leukocyte. The belief is expressed that this tumor should be classed among "endotheliomas."

METASTATIC TUMORS OF THE PERICARDIUM AND HEART

Metastatic tumors of the heart (Figure XIII-14) are much commoner than primary tumors. The literature does not give a correct account of the actual frequency of occurrence of metastasis to the heart, since usually only those instances are reported in which the metastatic growths were evident grossly. In my experience, foci of metastatic tumor cells

are occasionally encountered in the myocardium, if enough blocks are cut and examined histologically even though grossly no tumor is visible. Reuling and Razinsky (1941) also stated that, from recent studies of large series of autopsies, it is apparent that metastatic tumors of the heart occur more commonly than is ordinarily believed. McCandless and Fal-

oon (1948) diagnosed metastatic carcinoma of the pericardium by cytologic examination of the pericardial exudate.

Incidence. In the literature many reports of series of metastatic cancer are labeled merely metastatic to "the heart and pericardium" and often no distinction is made as to whether the heart, the pericardium or both are involved.

Brvant (1907) found 9 instances of metastatic tumor to the heart among 2492 autopsies at Johns Hopkins Hospital. Karrenstem (1908) reported 15 secondary carcinomas, 8 of which were to the pericardium and 4 secondary sarcomas of the pericardium among 6655 autopsies. Barden-

heuer (1924), among 1275 instances of malignant tumor, reported 30 secondary tumors (2.3 per cent) in the heart, the myocardium being involved only 8 times. Benjamin (1939) found an incidence of 0.5 per cent secondary carcinoma among 40,000 autopsies. Polha and Gogol (1936) recorded 220 secondary tumors in the heart among 46,072 autopsies (0.48 per cent) as collected from the literature. Lynburner (1934) found 52 among 8550 autopsies. Scott and Garvin (1939) stated that among 1082 instances of malignant disease appearing in a series of 11,100 autopsies, the heart was involved by metastasis in 79, the parietal pericardium in 61, the heart and parietal pericardium together in 22, and the heart or parietal pericardium, or both, in 118. Ritchie (1941), in an autopsy material of slightly

TABLE XIII-5
Source of 116 Secondary Tumors of the Pericardium and Heart
(Scott and Garvin, 1939)

Primary Tumor	Number of Cases	Metastasis to Heart	Metastasis to Parietal Pericardium	Metastasis to Both Heart and Parietal Pericardium	Metastasis to Heart or Parietal Pericardium or Both
Carcinoma of bronchus	115	30	28	15	41
Carcinoma of breast	45	3	13	0	16
Reteculum cell sarcoma	9	6	0	0	6
Melanoma	10	5	2	2	5
Lymphatic leukemia	11	6	0	0	6
Chloroma	3	2	0	0	2
Leiomyosarcoma	6	1	2	0	2
Carcinoma of bladder	25	0	1	0	1
Carcinoma of cervix	49	2	0	0	2
Carcinoma of colon	27	0	1	0	1
Carcinoma of esophagus	61	2	2	0	4
Carcinoma of kidney	19	3	1	1	3
Hypernephroma	12	1	0	0	1
Carcinoma of liver	21	2	1	0	3
Carcinoma of pharynx	9	1	0	0	1
Carcinoma of lip	5	1	0	0	1
Carcinoma of ovary	19	1	0	0	1
Carcinoma of pancreas	45	2	2	0	4
Carcinoma of prostate	56	0	2	0	2
Carcinoma of rectum	39	2	2	1	4
Carcinoma of stomach	201	1	1	0	2
Metastatic carcinoma (primary undetermined)	16	2	1	1	2
Neurofibrosarcoma	2	1	0	0	1
Retropentoneal sarcoma	2	0	1	0	1
Liposarcoma	1	1	0	0	1
Round cell sarcoma	4	1	0	0	1
Lymphosarcoma	13	1	1	1	1
Hodgkin's disease	22	0	1	0	1
Myelogenous leukemia	14	2	1	1	2
Miscellaneous *	221	0	0	0	0
	1,082	79	61	22	118

* Refers to a variety of tumors which in this series did not metastasize to the heart or pericardium.

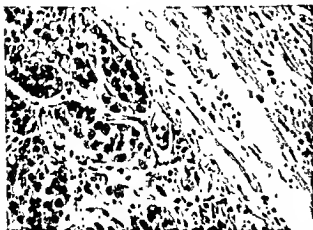


Figure XIII-15. Carcinoma metastatic to myocardium. The primary tumor was a carcinoma simplex of the breast. Hematoxylin and eosin. X 350.

over 3000, reported 16 metastatic tumors (0.53 per cent) in the heart and, in addition, 23 with metastasis to the pericardium. Lisa and associates (1941) collected from the literature reports of 119 tumors of the heart, of these 72 were primary in the heart and 47 were metastatic. Prichard (1951) found, among 4375 autopsies on patients with various cancers, 146 (3.4 per cent) with metastasis to the myocardium. The incidence of metastatic tumors varies from 5 per cent (Cassman *et al.*, 1955) to 26.6 per cent (Cohen *et al.*, 1955). Goudie (1955) stated that bronchogenic carcinomas metastasized in 31 per cent of his cases. Willis (1953) stated that fragments of growth carried in the systemic venous blood rarely become attached to the chordae or leaflets of the tricuspid valve or to other parts of the endocardial surfaces of the right chambers of the heart, and grow into branching or nodular masses. He also remarked that this occurs most frequently with teratomas of the testis, but also with alimentary and other carcinomas. Left-sided endocardial implants from tumor fragments carried in the pulmonary veins are still rarer.

Primary Site. Yater (1931) stated that metastasis to the heart has occurred from malignant neoplasms of all the main organs. Young and Goldman (1954) checked 476 consecutive autopsies having various malignant tumors for heart involvement, and found that the principal tumors which had metastasized to the heart were bronchogenic carcinomas, malignant melanomas, malignant lymphomas, and carcinomas of the pancreas and esophagus. DeLoach and Haynes (1953) reported

that, in a series of 2547 consecutive autopsies performed at Walter Reed Hospital, 980 had malignant disease, of which 137 had metastatic growth. Carcinoma of the lung had invaded the heart and pericardium more often than any other tumor. Table XIII-5, taken from Scott and Garvin (1939), is included to show the type and location of the primary tumor and the part of the heart involved by the metastatic tumor.

Types of Malignant Neoplasm. In many reports it is difficult to decide whether the involvement of the pericardium by bronchogenic carcinoma represents true metastasis or direct extension from the primary tumor to the pericardium.

Among 52 metastatic tumors in Lymburner's (1934) series, there were 36 carcinomas and 16 sarcomas, of which 6 were malignant melanomas. From Table XIII-5 it is clear that any malignant tumor may occasionally produce metastasis to the heart. Of all primary carcinomas, apparently carcinoma of the bronchus is the most frequent source of secondary tumors of the pericardium



Figure XIII-16. Malignant melanoma metastatic in myocardium. Hematoxylin and eosin. X 240. (WCGH, 58 P 369.)

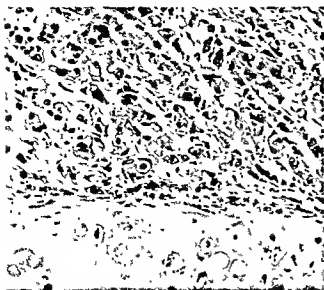


Figure XIII-17. Primary squamous cell carcinoma of bronchus which gave rise to implanted lesion on tricuspid valve (see Figures XIII-18 and 19). X 400. (WCCB, 50 P 628.) (Courtesy of Dr. F. C. Coller.)

and heart (Reuling and Razinsky, 1941). Among 66 instances of carcinoma of the lung in Herbut and Maisel's (1942) series, the heart was involved 8 times. Kaufmann (1922) stated that malignant melanotic tumors metastasize frequently to the myocardium. In my own experience, malignant melanoma and bronchogenic carcinomas are the malignant tumor which most frequently produces metastasis in the myocardium. (See Figures XIII-15 and 16.)

Among 81 metastatic tumors of the heart Raven (1948) found only 3 malignant melanomas. In his series the most common primary tumor was located in the breast.

A metastatic carcinoma of the pericardium which had produced a syndrome of constrictive pericarditis was reported by Wallace and Logue (1946). The primary tumor was a bronchogenic carcinoma.

A seemingly unique case, in which a primary myoblastoma of the region of the left groin had produced metastasis to the heart, was described by Khanolkar (1947). Grossly, the myocardium was sprinkled with tumor nodules, many of them being beneath the endocardium. These nodules seemed more numerous on the papillary muscles, giving the latter a peculiar beaded appearance. A testicular teratoma with extensive intracardiac metastases was reported by Watts (1947). Rabson's (1938) mesenchymal hemendothelioma produced metastatic growth in the right atrium.

Rarely a primary malignant tumor will break through a large vein and actually migrate into

the right atrium and ventricle, as reported in primary malignant tumors of the kidney by Oberndorfer (1907). (See also Kaufmann, 1922, for further references.)

Tumor implantation upon the mural endocardium or valvular endocardium is very rare. However, a few cases are on record which show that tumor cells may become implanted on the heart valves.

A pertinent case was reported by Coller and associates (1950). The primary tumor was a bronchogenic carcinoma (Figure XIII-17). Several clusters of soft delicate vegetations were attached to the chordae tendineae and the papillary muscles of the right ventricle and to the posterior leaflet of the tricuspid valve (Figure XIII-18). The vegetative growth was gray-white and cauliflowerlike. The mitral valve also contained two similar vegetative growths. Microscopically, nests of tumor cells were found in small groups or scattered throughout the dense fibinous and granular material (Figure XIII-19). It is interesting to speculate on whether these hearts have had primarily an acute vegetative (bacterial) endocarditis with secondary implantation of tumor cells. Coller and associates thought it probable that a certain amount of valvular damage is a prerequisite for tumor implantation. Rockenschau (1950) reported carcinomatous implants on the endocardium of the right ventricle in a patient with squamous cell carcinoma of the cervix.

Mode of Spread to Heart. The various modes of involvement of the pericardium and heart are discussed by Scott and Garvin (1939) and are indicated in Table XIII-6.

TABLE XIII-6

Frequency of Various Modes of Involvement of the Pericardium and Heart by Secondary Tumors, According to Scott and Garvin (1939)

Mode of Involvement	Site of Metastasis	
	Pericardium	Heart
Definitely hematogenous	8	37
Definitely by extension	25	18
Definitely lymphatic	3	0
Probably hematogenous	6	5
Probably by extension	2	1
Probably lymphatic	7	0
Combination of routes	2	4
Undetermined	8	14
	61	79



Figure XIII-18. Vegetation on tricuspid valve containing metastatic carcinoma, from primary bronchogenic carcinoma (cf. Figure XIII-17). (From Coller, F. C., Inkley, I. J., and Moragues, V.: Neoplastic endocardial implants, *Am. J Clin Path.*, 20:159, 1950. Courtesy of authors and The Williams & Wilkins Co.)

Portion of Heart Involved. Yater (1931) and Kirch (1927) and also Mahaim (1945) stated that the right side of the heart is more often involved than the left side. In Scott and Garvin's series, however, more secondary tumors occurred in the left side of the heart than in the right. In their cases the parietal pericardium was involved 61 times, the right atrium, 29; right ventricle, 31; left atrium, 29; left ventricle, 45, and interventricular septum, 11 times. In 6 cases neoplasm was found only upon microscopic examination. The endocardium alone may be involved. Herbut and Maisel (1942) mentioned 4 instances in which the mural endocardium, and 4 other instances in which the valvular endocardium was involved. Mahaim classified metastatic growths in the heart according to whether they involved the mural and valvular endocardium, the septal tissue, or other areas which were "silent."

A metastatic carcinoma to the interventricular septum, diagnosed clinically because of a pulse rate of 26 to 28 per minute was reported by Rosler (1924). The primary carcinoma arose from the skin of the cheek.

"Marantic Endocarditis" (Nonbacterial Thrombotic Endocarditis). The valvular endocardium of patients who die of cancer may have changes called *marantic endocarditis*. According to Eger (1941), Guder found 169 instances of recent verrucous endocarditis

among 12,705 autopsies. Among these 169 autopsies were 43 instances of cancer, 40 of which revealed no evidences of an acute infectious disease. Such an endocarditis occurring in cancer patients in the absence of an acute infectious process, is sometimes referred to as "cancer endocarditis" (Eger). The endocardial changes are explained as follows:

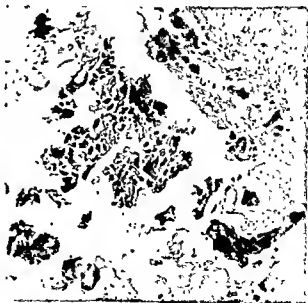


Figure XIII-19. Photomicrograph of vegetation shown in Figure XIII-18. X400. (WCGH, 50 P 628.) (Courtesy of Dr. F. C. Coller.)

shortly before death of the patient, toxic substances are absorbed. This causes an activation of the mesenchyma and also damages the endothelial lining of the heart valves. In the region of these defects, the blood plasma extends into the valvular tissues and causes a fibrinoid degeneration with consequent formation of thrombi. Eger concluded that split products of the carcinoma are toxic and cause

the allergic reaction. (See also Allen and Sirota, 1944.)

Eger also described interstitial myocardial granulomata, consisting principally of histiocytic cells, in patients who died of cancer. Among 34 hearts with endocarditis, from patients with carcinoma, such changes were found 8 times. In not a single instance were typical Aschoff bodies recognized

CYSTS OF THE MYOCARDIUM AND HEART VALVES, AND DIVERTICULA

Epithelial Cysts

Simple epithelial cysts (Figure XIII-21) also occur within the heart but are very rare. Davidsohn in 1938 was able to find only 3 instances in the literature, to which he added a fourth. These cysts were encountered as incidental findings.

Stoeckenius (1919) reported a pea-sized cyst in the posterior papillary muscle of the left ventricle. The inner surface of the cyst was lined by ciliated epithelial cells, varying from columnar to cuboidal to flat cells, the latter resembling the lining endocardial cells. In some cells the nuclei were displaced to the periphery, producing a resemblance to goblet cells. He attempted to explain these cysts on the basis of persistent unused minute cavities, dating back to the embryonal period when the cavity of the heart had the structure of a sponge. Kolatschow (1933), who reported a cyst (21 by 18 by 17 mm.) close to the anterior papillary muscle of the left ventricle, suggested either heterotopic glandular structures or misplaced epicardial lining cells as the possible origin of this cyst. (See also Leicher, 1948.)

De Châtel (1933) found 2 cysts lined by squamous cells in the interatrial septum of a newborn girl.

Davidsohn found a cyst measuring 10 by 5 by 4 mm. on the posterior wall of the left ventricle within the posterior papillary muscle near its tip. It was an incidental finding in a 64-year-old woman, who died of general peritonitis following operation for perforation in adenocarcinoma of the cecum. Microscopic examination of the cyst disclosed its inner surface to be lined by two layers of epithelial cells, covered by cilia. Mayer's mucicarmum stain showed areas staining deep red at the periphery of the cystic cavity, adjacent to

the lining cells. Davidsohn called attention to the similarity in structure between such a rare epithelial cyst of the heart and the not uncommon esophageal cyst which is lined with a columnar, frequently ciliated, epithelium or with squamous cells. The lumen of these cysts is always completely separated from the lumen of the esophagus. It is accepted that the esophageal cyst is caused by a disturbance in the separation of the trachea from the intestinal tract. Davidsohn pointed out that, whereas such an explanation for the esophageal cysts is convincing, there is no bridge that would permit the applica-

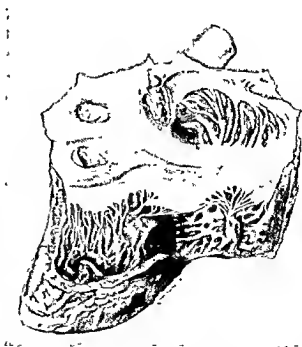


Figure XIII-20. Thrombus attached to reticulations of right atrium just inferior to mouth of superior vena cava, containing carcinomatous embolus from primary carcinoma of cervix. (Drawing by Louise Horne, Wayne County General Hospital.)



Figure XIII-21. Congenital cyst of myocardium X 150. (WCGH, 45 P 191 A.) (Courtesy of Dr. B. E. Stofer.)

tion of this hypothesis to the epithelial cysts of the heart.

Leighton and associates (1950) found squamous epithelial cysts in the heart of an infant at the root of the septal leaf of the tricuspid valve and the adjacent septum, along with a saccular deformity. The interventricular septum was patent. The cysts were multilocular and were lined by non-keratinizing stratified squamous epithelium. Some of the cystic spaces contained an amorphous debris and shrunken cells with clear cytoplasm and pyknotic nuclei. There were also cystic changes in the ovaries and breasts.

Sachs and Angrist (1945) reported a small cyst situated in the center of the left ventricular wall, measuring 0.9 cm. in diameter. It was completely surrounded by cardiac muscle and did not cause any discernible bulging of the muscle toward either the epicardial or the endocardial surface. The contents of the cysts were gelatinous and translucent, with a pale green tint. On microscopic examination, the inner epithelial layer was tall, columnar and ciliated for the most part, but cuboidal in other areas.

The authors suggested that such cysts arise

through the heterotopic inclusion and sequestration of entoderm during the formation of the primitive foregut and single-chambered heart. Bayer (1940) described a cyst arising just beneath the epicardium close to the apex of the heart. The cyst was lined by endothelial cells and was interpreted as originating from misplaced epicardial cells. He also described a cyst in the myocardium lined by ciliated epithelial cells, in a patient who had died of carcinoma of the large intestine. This cyst was interpreted as arising from misplaced epithelium of the bronchial tree.

Summary. If microscopically a number of small glandlike structures are encountered in the heart, especially in the region of the atrio-ventricular node, it is most likely that they represent misplaced pericardial lining cells. If they form tumors, they must then be interpreted as mesotheliomas. If cysts are present which are lined by cells of questionable origin, they may also be regarded as arising from mesothelial cells. If they are ciliated, it

is thought that they may have arisen from misplaced epithelium of the bronchial tree. If the cells are squamous in type, they may have been derived either from misplaced ectodermal or from entodermal cells which had undergone metaplasia. From a review of the reported instances of cysts in the myocardium, one is struck by the fact that in some of these patients, in addition to the cysts, a primary carcinoma was also present, commonly located in the gastrointestinal tract. In the cases cited, the authors discussed, but always ruled out, the possibility that the cysts represented metastatic lesions. (See also Mesotheliomas of the Heart.)

Blood Cysts (Telangiectases)

Blood cysts (telangiectases) are often found on the heart valves of newborn infants. According to Levinson and Learner (1932), they were recorded as early as 1844 by Elsaesser and 1857 by Luschka. They are described as small, circumscribed, elevated, dark red nodules which appear grossly as cysts filled with blood. They are seen most commonly on both the mitral and tricuspid leaflets, usually vary from pinpoint to pinhead size and rarely exceed 1 mm. in diameter. They vary in number, usually from 2 or 3 to 10 or 15, but as many as 30 have been reported in one heart. The nodules project above the atrial surface of the atrioventricular leaflets near the free margin between the edge and the line of contact or closure. On the semilunar cusps the nodules project into the ventricle and are located at, or very close to, the line of attachment of the cusps.

The rare occurrence of a hemangioma (blood cyst?) was reported by Prichard (1951) in the right atrium in the region of the foramen ovale in a 38-year-old white man.

Valves Involved. Table XIII-7, taken from Jonsson's (1916) communication, discloses the relative frequency of the involvement of the valves.

Microscopic Appearance. On histologic examination the nodules appear on cross-section as spaces filled with red blood corpuscles. These spaces are lined by a single layer of

TABLE XIII-7

Distribution of Blood Cysts (Telangiectases) on Heart Valves in Jonsson's (1916) Series of Newborn Infants

Valves Involved	Valves Showing Nodules (Cysts)	Number of Cases
Mitral, tricuspid, pulmonary and aortic	4	2
Mitral, tricuspid and pulmonary	3	2
Mitral and tricuspid	2	23
Tricuspid and pulmonary	2	1
Tricuspid and aortic	2	1
Mitral and aortic	2	1
Mitral	1	7
Tricuspid	1	6
Aortic	1	1
Pulmonary	1	1
Total		45

endothelial cells, in appearance similar to the surface of the endothelium of the valve leaflet. Near the attachment of the valve to the myocardium a few blood vessels are instantly seen, although in the body of the leaflet no blood vessels are found.

Origin. Several views have been expressed regarding the origin of these cysts (telangiectases). Some authors believe that they represent extravasations of blood and should be classified as hematomas. Others believe that they represent either true angiomas or, perhaps better, hamartomas, while still others think that these cysts represent dilated blood vessels. Another opinion holds the cysts to be spaces filled with blood, the result of blood pressed into crevices running from the surface of the leaflet into the stroma forming the leaflet. According to Jonsson (1916), the cysts develop when passing blood accumulates within these spaces or potential spaces. Development of cysts depends on the specific structure of the leaflet as well as upon the character of the tissue of the leaflet. Levinson and Learner (1932) concluded that there is no pathologic significance to these cystic nodules. They are to be regarded as a common anatomic finding. Boyd (1949) believed that blood cysts are commonly present on the heart valves of infants. From a study utilizing serial sections, he supported the explanation that they result from



Figure XIII-22. Fibrinosanguineous pericarditis resulting from infiltration by monocytic leukemia (WCGH 49 P 491.)

blood being pressed into crevices on the ventricular surfaces of the cusps. Subsequent fusion of the mouths of the crevices forms the blood cyst.

Diverticula of Heart

True Diverticulum. True diverticula of the heart were recorded by Arnold (1894) and also by Mahrburg (1930). They described fingerlike outpouchings of portions of the left ventricle, which were well separated from the surrounding structures outside the heart, or which were either separated from the heart, or had extended through the opening of the diaphragm to the anterior abdominal wall. The wall of these outpouchings consisted of cardiac muscle and were lined by endocar-

dium. Therefore, they were classified as true diverticula.

False Diverticula. A false diverticulum was recorded by Bayer (1940). It was located at the apex and had caused adhesions between both leaves of the pericardium. It was thought that the original lesion was misplaced endocardium, which because of necrosis of proliferated endothelial cells, formed a cystlike structure, still communicating with the left ventricle. The cystic structure gradually became larger and extended into the pericardial sac. The result was an outpouching of the endocardial structures into the pericardium. It is difficult to decide whether this false diverticulum may be interpreted as an aneurysm of the heart.

LEUKEMIA AND ALLIED DISEASES

In the discussion of leukemic involvement of the heart, an attempt is made to distinguish between simple microscopic leukemic infiltration and leukemic infiltration which has assumed the proportions of a neoplastic mass. Yet, from the literature, it is sometimes difficult to decide to which classification the relevant report belongs. It is also

often difficult to decide whether a given tumor should be classified among leukosarcoma (sarcoleukosis, see Hirschfeld, 1925), lymphosarcoma, chloroma or chlorosarcoma, or myelosarcomatosis. Whatever classification is adopted, whatever the true nature of these lesions may be, it must be emphasized that the pericardium (Figure XIII-24) and myo-

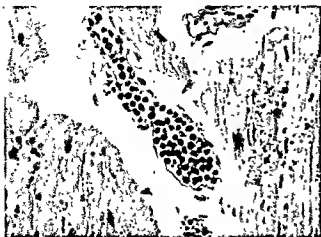


Figure XIII-23. Myocardium in lymphoblastic leukemia. Note blood vessel filled with immature leukocytes. Iron-hematoxylin. X 125.

cardium are often involved in these conditions.

Leukemia

According to Kirch (1927) leukemic infiltrations of the myocardium are found only occasionally. They occur in both lymphatic and myeloid leukemias. These infiltrations may be confined to the stroma and may be confused with myocarditis. I have seen severe leukemic infiltration of the myocardium in leukemia patients who died unexpectedly. Often the pericardium is also involved (Figure XIII-22). Wendkos (1941) described, as the earliest and outstanding manifestation, massive pericardial effusion in a patient with leukemic involvement of the pericardium.

Leukemic infiltration of the myocardium (Figures XIII-23 and XIII-24) is much more common than was previously assumed. This can be easily explained by more careful histologic examinations of the myocardium.

Thus, Aronson and Leroy (1947) concluded that the heart is frequently involved in leukemia. Furthermore, Wintrobe and Mitchell (1940) reported the occurrence in patients with leukemia of initial symptoms suggesting cardiac disease. One of their patients disclosed, at autopsy, a myeloid chloroma with cardiac involvement.

Kirschbaum and Preuss (1943) studied 123 fatal cases of leukemia and found the heart involved in 43 (34 per cent). The leukemic cells were encountered within the capillaries and in the interstitial tissue between the myocardial

fibers. The heart was involved in 6 of 11 patients (54 per cent) with acute lymphatic leukemia. The highest percentage of cardiac involvement was found in acute stem cell leukemia. Of 23 such instances, leukemic infiltrations in the myocardium were encountered 14 times (61 per cent). As stated above, Wendkos (1941) reported massive involvement of the pericardium and myocardium in a patient with acute lymphatic leukemia who died unexpectedly. Burnett and Shimkin (1954) found that 26 per cent of their patients with leukemia had involvement of the heart.

Among 95 instances of various forms of leukemia which were studied at Michael Reese Hospital and carefully examined microscopically for the presence or absence of myocardial involvement, leukemic infiltrations were found in 34 hearts (36 per cent). The above figures, therefore, indicate that the myocardium is commonly involved in leukemia.

Reim (1916) reported an instance of acute lymphatic leukemia with tumorous nodules in the endocardium, in which the question arises whether the classification should not be lymphosarcomatosis or, perhaps, sarcoleukosis. Low (1910) reported such an instance of myeloid cell infiltration at the base of the interventricular septum.

While leukemic infiltrations are thus commonly encountered, Forkner (1938) has stated that the progressive heart failure sometimes observed in patients with leukemia is



Figure XIII-24. Leukemic (lymphoblastic) infiltration of myocardium. Hematoxylin and eosin. X 100.



Figure XIII-25. Nodular infiltration of atrial septum above tricuspid valve, in Hodgkin's disease. (WCH, 52 A 183.)

caused in all probability by myocardial degeneration, anemia and anoxemia.

Three apparently unique cases may be quoted here. Costa (1931) attributed rupture of the left atrium of the heart to leukemic infiltration (myeloid leukemia). Puech and associates (1932) reported unexpected death in a patient with acute leukemia. At autopsy, a leukemic thrombus was found completely filling the ventricles of the heart. Koberle (1937) described leukemic infiltrations in the heart valves.

Chloroma and Lymphosarcoma

Chloromas also involve the heart. A typical instance of myeloid chloroma was described by Mieremet (1914). Green nodules were found in the anterior wall of the left ventricle and posterior wall of the right ventricle. Lymphosarcoma involves the pericardium much more often than the myocardium.

Among 23 cases of metastasis to the pericardium in Mieremet's series, there were 5 lymphosarcomas. Among his 16 instances of metastasis to the myocardium, there was only 1 lymphosarcoma, but the gross data were incomplete. Bardenheuer (1924) found a primary lymphosarcoma of the ileum, which had metastasized to the right atrium and right ventricle and had produced severe stenosis of the tricuspid orifice. Young and Goldman (1954) and Cohen and associates (1955) stressed the relatively high incidence of involvement of the heart by malignant lymphoma.

As far as leukosarcomas are concerned, Forkner (1938) states that leukosarcoma, when situated as it is so often, within the anterior mediastinum, frequently invades the pericardium and also the myocardium.

Myeloma

Myelomas also may produce metastatic nodules in the myocardium (Lichtenstein and Jaffé, 1947).

Carlisle (1938) found 2 nodules, each the size of a bean, in the wall of the right atrium in a patient with myeloma. Pacey and Riach (1931) found, in a patient with multiple myeloma, a number of white nodules at the apex of the heart, which represented extramedullary metastasis.

Hodgkin's Disease

Hodgkin's disease also involves the heart (Figures XIII-25 and 26). Extension of mediastinal masses into the pericardium and myocardium is occasionally seen in routine postmortem material, though many such occurrences are not reported.

Schlagenhauser (1919) reported 3 cases of Hodgkin's disease of the gastrointestinal tract. In 1, the heart was of a yellow color and presented an irregular speckled appearance. Histologically, the myocardium showed typical granulomatous tissue with Sternberg-Reed cells. Silk (1933), in a general review of myocarditis, mentioned a case. Dalous, Fabre and Pons (1936) reported, in a 25-year-old man with Hodgkin's disease of the mediastinum, that the myocardium showed a number of white spots which histologically consisted of the specific type of granulation tissue. It is interesting to note that muscle giant cells were also present which were definitely distinguished from the Sternberg-Reed type of giant cell. The patient had died suddenly. Without giving any reference, these authors quoted a case of Hodgkin's granuloma in the heart, reported by Barre and Desnos. Krueger and Meyer (1936) reviewed 60 cases of Hodgkin's disease, including 16 autopsies. The ventricular myocardium was involved twice and the right atrium once. McAlpin (1937), in a review of 23 autopsies found a record of nodules in the myocardium in 2 instances. Harrell (1939) reported an instance of fulminating Hodgkin's disease in which the pericardium and myocardium were involved, and Ritvo (1940) also reported an instance with in-

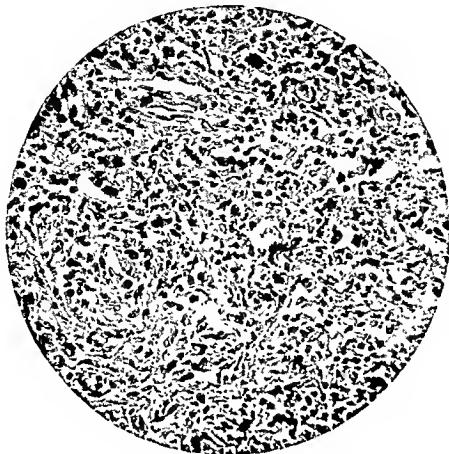


Figure XIII-26. Hodgkin's disease infiltrating heart. Hematoxylin and eosin. X 300. (WCGH, 435-38.)

involvement of the pericardium and myocardium. The pericardium and the right atrium were involved in the case reported by Garvin (1941). The Hodgkin's granulomas projected into the atrial cavity as a polypoid mass.

Setzu (1942) stated that he was able to collect only 10 instances of involvement of the heart in Hodgkin's disease. He described an additional case in which both the pericardium and myocardium had characteristic Hodgkin's granulomata. Most of the changes in this instance were encountered in the pericardium where the nodules were well circumscribed and only a few had fused.

The occurrence of numerous polypoid growths microscopically characteristic of Hodgkin's disease covering the endocardium of the left ventricle, especially between the columnae carneae, was reported by Catsaras and Patsouri (1941). These authors interpreted the polypoid lesions as implantations from the blood stream.

Rast and associates (1945) encountered an instance with involvement of the epicardium by numerous gray-white nodules which microscopically were characteristic of Hodgkin's disease. Extensive involvement of the mediastinum was also present.

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Lesions of the Aorta

IRA CORE

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I. ATHEROSCLEROSIS

ATHEROSCLEROSIS is by far the most common affliction of the aorta but is by no means limited to it. Indeed the clinical importance of atherosclerotic involvement of coronary, cerebral and iliofemoral arteries far exceeds that of the process in the aorta. Nevertheless, the basic changes at all sites are the same and they are most readily visualized in the aorta. Atherosclerosis has been defined as a "disease primarily of large arteries, characterized by plaque-like intimal deposits which contain neutral fat, cholesterol, lipophages and sometimes blood or other evidence of hemorrhage" (Committee on Nomenclature, 1955). It is clinically the most important of the degenerative and sclerosing processes, producing thickening or hardening of arteries or atherosclerosis (Hueper, 1944, 1945; Katz and Stamler, 1953). Unfortunately, indiscriminate use of the latter and older term has resulted in ambiguity and confusion (Rabson, 1954; Magarey, 1955). As defined by Lobstein, arteriosclerosis also in-

cludes Monckeberg's medial calcification as well as arteriolar hyperplasia and sclerosis (Katz and Stamler, 1953).

The intimal disease has far-reaching clinical significance since it ranks among the leading causes of death. This lesion affecting the arteries supplying the brain, heart, kidneys and legs is responsible for considerable human incapacity. Despite medical progress that has led to increase in human longevity, the problem of atherosclerosis is as yet unsolved and has created an intense interest on the part of investigators. Moreover, longevity alone is inadequate to account for the manifold increase in incidence of fatal coronary heart disease observed in the United States and the United Kingdom within the past generation (Hueper, 1944, 1945).

Historical

Descriptions of calcified or ossified arteries by early anatomists constitute the first recorded evidence of atherosclerosis (Lee and

956). However, it is apparent from the examination of Egyptian mummies of the 10 B.C. to 525 A.D. that the disease was present in the written accounts and was then as common as it is in modern civilization (Roser, 1911). The following brief account has been taken from the historical review of Long (1933).

In the 18th century Haller indicated the close relationship of soft atheromatous lesions and syphilis. Both Lancisi and Morgagni have recognized that syphilis contributed to the development of atherosclerosis. Arteries were attributed to atheromatous changes by Scarpa. In the 19th century, the nature of the lesion in the intima was recognized (Hodgson (1815); Lobstein (1833)). The term *arteriosclerosis* for all conditions characterized by hardening and induration of arteries (Cruveilhier (1829-1842) focused attention on the frequency of thrombosis. One of the contemporary thoughts (Duguid and MacCallum (1952)) stems from Rokitsky (1841) who attributed intimal plaques to the presence of superficial deposits of fibrin. Virchow (1858) is generally acknowledged as the originator of the popular 'imbibition' thesis. He attributed the disease basically as inflammatory and suggested for it the term *endarteritis obliterans*. Gull and Sutton (1872) delineated the disease as atherosclerosis the diffuseness of small arteries which Johnson first described in relation to Bright's disease. Histologic recognition of syphilitic mesenteric arteries from Welch (1875) and Dohle (1883) suggested that intimal thickening was a compensation for the dilatation of arteries with age. Jores (1898) called attention to the quantity of elastic tissue to be found in the intimal plaques. Early in the 20th century Marchand (1904) suggested the presence of atherosclerosis to distinguish the condition from other arterio-vascular lesions that result in hardening of the arterial wall. Klotz (1911), however, had called attention to the primary nature of medial changes resulting from arterial, toxic or infectious causes. The prevalent concepts date largely from the concepts of Ambschläger (1913) and Lechmann (1921) to which further reference will be

Appearance in Relation to Age

Although, in general, atherosclerosis increases in severity with age, for any given age-group there are so many individual exceptions and so much variation in different geographic areas that the disease cannot be regarded as an invariable consequence of aging (Katz and Stamler, 1953). Those changes which are properly attributable to senescence include a gradual diffuse distension and tortuosity most noticeable in the large arteries, a progressive increase of intimal fibrous tissue and an accumulation of finely divided calcareous material in the media (Ophüls, 1933; Blumenthal et al., 1950; Buck and Rossiter, 1951). Ophüls (1933) stated that at about 40 years of age, elongation of the arteries has nullified the elastic tension found in younger persons; beyond this age, further elongation results in tortuosity. The absence of elasticity in the dilated and tortuous arteries of aged persons was formerly attributed to a loss of elastic tissue but is more accurately ascribed to a loss of elastic reserve since chemical analysis shows a normal quantity of elastin (Hass, 1943).

Subintimal accumulations of lipid-staining material occur early in childhood, are frequent at 6 months and are practically constantly found after 3 to 4 years (Zinslerling, 1925; Holman et al., 1958). They generally take the form of slightly elevated, round or oval, yellow streaks or spots (Lange, 1924). They are most common at the base of the aorta just above the sinuses of Valsalva where they lie transversely. More distally they form superficial, longitudinal streaks on the posterior surface of the thoracic and abdominal aorta. There is no predilection for the lower abdominal segment and, as Ophüls (1933) indicated, there is no agreement concerning the relation of such reversible lesions to atherosclerosis. Most students of the process accept them as the first manifestation of atherosclerosis which develops in more typical fashion as a reaction to imbibed lipid material (Klotz, 1915b; Zinslerling, 1925; Griffin et al., 1955). Studies of the evolution of experimentally induced lesions in rabbits



Figure XIV-1. Portion of thoracic aorta. Note large "pearly white" atherosclerotic plaques, especially about the ostia of the segmental vessels. The smaller lesions, almost pure lipid in composition, arise abruptly from the intimal surface.

provide strong support for this viewpoint (Anitschkow, 1933).

Microscopically, these early lesions are characterized by local subendothelial infiltration of the intima by aggregated masses of fine anisotropic lipid droplets. This material, rich in cholesterol, lies both in and between the cells, and seems to be largely restricted to the intima by the "barrier" of the internal elastic lamella (Anitschkow, 1933).

By the end of the second decade some degree of atherosclerosis is present in all aortas. The typical plaque-like lesion (Figure XIV-1) results from progressive reactive thickening of the intima. Accordingly, sharp distinctions between prominent fatty streaks and early atherosclerotic lesions cannot always be made. However, after age 30, plaques of fibrous and lipid composition form

a progressively greater part of the disease. Early lesions are composed of small, round or oval, yellow spots which project slightly. They measure only a few millimeters in diameter but tend to fuse and form larger irregular plaques. The posterior wall of the thoracic and abdominal aorta, especially about the orifices of the segmental vessels, is the site of predilection. The process is most advanced in the lower abdominal aorta, and the ascending aorta and arch are relatively spared. Moreover, it is often observed that most of the disease that is present in the proximal aorta is lipid in character, even when sclerotic plaques predominate distally. Similarly, the extent and severity of the intimal disease is far greater in the arteries of lower extremities than in those of the upper (De Takats and Pirani, 1954).

Histologically the plaques consist of acellular fibrous tissue with variable quantities of lipid both intra- and extracellularly. In the distinctive pearly white plaque (Figure XIV-2), the fatty component, amorphous and crystalline, lies in the depths of an intimal lesion capped by a relatively thick hyaline sclerotic layer rich in thin elastic fibers. Although such lesions do not stain when Sudan III is applied to a gross specimen of aorta, they are often rimmed with more superficial sudanophilic material which suggests peripheral extension of the plaque. Growth also occurs by superficial accretion since deposits of lipid may be superimposed upon fibrous plaques. There is no relation between the quantity of lipid and the amount of fibrosis in the intimal lesion. Related to the presence of the plaque are thinning and attenuation of the underlying media, fraying and disruption of the internal elastic lamina and a local increase of vasa vasorum. Hemorrhages, so frequently noted in atherosclerosis, undoubtedly arise from such channels and leave vestiges which contribute to the content of the lesion (Winternitz *et al.*, 1938; Geiringer, 1951).

Contributory Factors

Irregularities in the distribution of atherosclerosis, particularly under special circumstances, provide helpful clues to some of the

factors which contribute to it. Immunity of the venous circulatory system to this process suggests the importance of systemic arterial blood pressure. Confirmatory evidence is provided by the relative sparing of the pulmonary arteries except in conditions associated with prolonged pulmonary hypertension and by increased severity of the disease both in human beings and in experimental animals with systemic hypertension (Gubner and Ungerleider, 1949, Tobian, 1955). A reasonable explanation for the special vulnerability of the posterior aortic wall is found in the effect of pressure. Fixation and splinting by the vertebral column and by segmental vessels limit elastic recoil and augment the impact of pressure of the pulse upon this

portion of the aortic wall. Conversely, the mobility of the aortic arch explains the relative sparing of this segment. Commonly plaques are noted on the ventricular aspect of the anterior leaflet of the mitral valve which bears the brunt of left ventricular systole. In coarctation of the aorta, intimal disease is more advanced proximal to the narrowing (Moschkowitz, 1942); distally, a plaque marks the site of impingement of the jet of blood emerging from the stenotic area (Edwards *et al.*, 1948). Erect posture and hydrodynamic pressure probably explains the augmented sclerosis in the lower aorta and in the arteries of the lower extremities (DeTakats and Pirani, 1954).

Early involvement of the aortic ring near

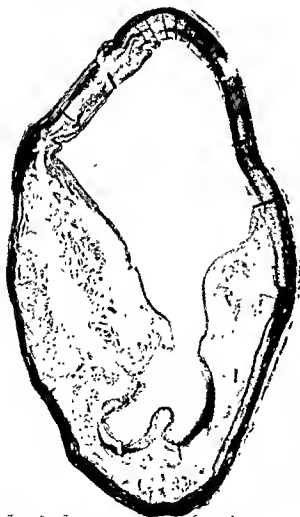


Figure XIV-2. Transection of aorta. Loosely structured and fragmented intimal plaques bulging into the lumen, probably more than they do in life when they are compressed by the force of the circulating blood. Note thinning of the heavily stained media underlying the plaques. X 4.



Figure XIV-3. Severe atherosclerosis of aorta. Note isolated and coalescent plaques, ulcerations and thrombi.

the insertions of the semilunar cusps (Griffin *et al.*, 1955) suggests the importance of mechanical trauma; similar inferences pertain to lesions about the ostia of the segmental vessels.

Syphilis commonly produces an aortitis involving the arch which results in medial scarring and intimal fibrosis. Superimposed atherosclerosis is frequent (Anitschkow, 1925) and, unlike uncomplicated atherosclerosis, is more advanced in the proximal aorta. Similarly, the aortitis that less commonly complicates acute rheumatic fever may result in intimal thickening which predisposes to atherosclerosis (Pappenheimer and Von Glahn, 1924). Of greater clinical significance, however, is the propensity of the rheumatic inflammatory process to involve the coronary arteries (Karsner and Bayless, 1934; Saphir and Gore, 1950).

Experimentally, other factors have been shown to be important in contributing to atherosclerosis, but their relation to the human disease requires elucidation. Chronic deprivation of pyridoxine in monkeys (Rinehart and Greenberg, 1949, 1956) and dogs (Mushett and Emerson, 1956) has resulted in formation of intimal plaques, essentially devoid of lipid. Deficiency of the sulfur-containing amino acids exerts an essential conditioning influence on cholesterol-atherogenesis in monkeys (Mann *et al.*, 1953). Moreover, it is possible that the administration of cholic acid may augment atherogenesis in the rat as a result of draining the body reserves of sulfur (Fillios *et al.*, 1956). Deficiency of choline has resulted in medial calcific lesions in the aorta of the rat (Hartroft *et al.*, 1952) but its role as a cause of intimal lesions has been contested (Hueper, 1945).

Chemistry

Cholesterol was recognized as a component of atheromatous material in 1857 by Mettenheimer (Wells, 1933). According to Wells, the question of whether the deposition of lipid is primary has been a point of dispute (Virchow, 1856; Thoma, 1883; Jures, 1898; and Klotz, 1911). Barr (1953) suggested that the fatty deposits were secondary to primary intimal overgrowth, a viewpoint reasserted by Rinehart and Creeoberg (1949,

1956) who stressed the accumulation of mucopolysaccharide. Aschoff (1914, 1924) proposed the more widely accepted "permeation" theory that circulating plasma lipids infiltrate the intima and by their accumulation incite a reactive proliferative process to produce the intimal plaques of atherosclerosis. The process is facilitated by an ill-defined "physicochemical" degenerative change in the supporting ground substance of the intima. Substantial support for this viewpoint is provided by (1) the induction of atherosclerosis by hypercholesterolemia in rabbits (Anitschkow, 1933), monkeys (Mann *et al.*, 1953), dogs (Steiner *et al.*, 1949; Bevans *et al.*, 1951), and rats (Wissler *et al.*, 1954; Fillios *et al.*, 1956), (2) its accentuation by hypertension (Tobian, 1955) as well as by processes or conditions which damage the vessel wall (Anitschkow, 1933; Wartman, 1955), and (3) chemical analysis of the lesions in atherosclerosis. Hirsch and Weinhouse (1943) and Hirsch and Nailor (1956) have shown the similarity of the lipid components of blood plasma and of early plaques. With older lesions, the "total cholesterol" increases at the expense of phospholipids and neutral fat, a process attributable to their selective removal (Buck and Rossiter, 1951). The chemical change is accompanied by a morphologic reorganization from a superficial intimal lesion rich in foam cells to a plaque capped with fibrous tissue and characterized by a necrotic center rich in extracellular lipid material (McMillan *et al.*, 1955).

Pathogenesis

It is generally accepted that the inner layers of arterial walls are nourished by seepage of plasma through the intima. Kellner (1955) has demonstrated that *in vivo* the normal capillary wall permits the passage of appreciable quantities of protein and lipid which are then collected by the lymphatics. Qualitatively similar seepage through arterial walls is prevented by their more substantial structure; however, the endothelial lining, no different than that of the capillaries (Anitschkow, 1933), does permit access of constituents of the plasma to the intima. Perfusion

of arterial segments *in vitro* (Evans *et al.*, 1951; Wilens, 1951) has demonstrated this process and indicated its significance in atherogenesis by formation of intimal lipid deposits. Mere mechanical filtration would seem to eliminate the chylomicrons from consideration. The other lipid fractions are of molecular size in the form of lipoprotein complexes (see below). While much remains to be ascertained about the factors which lead to the segregation of fatty substances from other plasma constituents, the physical properties (molecular size, solubility, stability, etc.) of the lipoproteins must be of importance. In these experiments the rate of intimal accumulation of lipid far exceeds anything observed in life. An increase in permeability seems a reasonable explanation but there is also a basis for suggesting that a "clearing" mechanism exists in the wall of the living vessel. Changes in the composition of lipid in atheromatous deposits, with age (Hirsch and Weinhouse, 1943), indicate a vital process which is ineffective in dealing with cholesterol. Even the latter shortcoming is relative since regression of plaques does occur in rabbits, if sufficient time is allowed (Anitschkow, 1933). Accordingly, atherosclerosis may be the consequence of permeation of lipid in excess of the "clearing" capacity of the vessel wall. The augmenting effect of inflammation, injury or deficiency of essential metabolic component could be mediated by impairment of the "clearing" mechanism.

Local conditions, already mentioned, explain the focal plaque-like nature of the intimal disease. In rabbits, staining of the aortic wall by trypan blue occurs precisely at those sites which are most vulnerable to deposition of lipid (Anitschkow, 1933). Similarly the selective uptake of colloidal thorium by intimal plaques in the rabbit demonstrates greater permeability at these foci (Duff, McMillan and Lautsch, 1954). Cortisone and hyaluronidase have a more general influence on permeability; administered to rabbits, they respectively inhibit or augment cholesterol atherogenesis (Wang *et al.*, 1955).

As Hueper (1956) has indicated, objections can and have been made to other theories of pathogenesis. Too many exceptions occur

at either end of the age scale for senescence to be considered seriously as a cause of atherosclerosis (Katz and Stamler, 1953). In primary medial disease (Duff, Brechin and Finkelstein, 1954), one does not take into account the frequent intimal lesions without change in the subadjacent media. Organization of mural thrombi (Duguid and Anderson, 1952) undoubtedly does occur but is a plausible explanation in only a small number of cases and then usually in advanced atherosclerosis. Leary's (1941) concept of lipophagic invasion of arterial intima leaves too many riddles and has not been confirmed with isotope-labelled macrophages (Simonton and Gofman, 1951). Finally, Hueper's (1956) colloidal macromolecular theory requires substantial documentation. The significant "colloidally unstable cholesterol complexes of low density" have not been characterized. Indeed those changes which have been established in plasma cholesterol *per se* or in the lipoproteins (see below) are quantitative and not qualitative. The premise that constituents of low density in the plasma of molecular or even of macromolecular size show characteristics of laminar flow in the circulation, and are displaced to the periphery, seems unlikely. Enormous centrifugal forces are required to demonstrate differences in density in molecules and protein. Finally the normal endothelium is permeable to proteins and lipids (Kellner, 1955) and it is not necessary to postulate anoxic or other disturbances to account for it. It follows, of course, that these same considerations apply to the other experimentally administered macromolecular substances which produce intimal lesions in animals.

Lipid Metabolism

Even though it has been established, for some species at least, that cholesterol can be synthesized by the aortic wall (Wethessen, 1954), quantities so formed are not sufficient to explain the deposits which characterize severe atherosclerosis (Frantz, 1955). These must have their origin in the blood, and considerable evidence has accumulated showing that the frequency and severity of athero-

sclerosis varies with the serum cholesterol level (Gubner and Ungerleider, 1949). Certain diseases, characterized by hypercholesterolemia out of proportion to elevation of other fractions of blood lipids, have been associated with an augmented tendency towards atherosclerosis both in incidence and severity. These include diabetes mellitus, lipid nephrosis, hypothyroidism and essential familial hypercholesterolemia and xanthomatosis (Gofman *et al.*, 1954; Piper and Orrild, 1956). Comparative geographic studies have shown striking differences in the incidence of atherosclerosis that may be correlated with parallel differences in the "normal" blood cholesterol levels. These in turn reflect the content of lipid and cholesterol of the diet habitually consumed by the population group (Katz *et al.*, 1955; Keys, 1956; Tejada and Gore, 1957). Parenthetically, not only is there a relationship between intake of fat, levels of cholesterol, and atherosclerosis, but it appears that saturated neutral fats and fats of animal origin have greater significance than other forms (Kinsell *et al.*, 1953; Bronte-Stewart *et al.*, 1956). From both human and experimental material, it is obvious that there is no simple relation between elevated serum cholesterol and atherosclerosis. In familial hyperlipemia, the level of cholesterol is increased but not to the same degree as the other lipid components and there is not the propensity to atherosclerosis that characterizes familial hypercholesterolemia and xanthomatosis (Thannhauser, 1950; Boggs *et al.*, 1957).

Experimentally Hirsch and Nailor (1955) created the analogous situation and found similar results in rabbits fed diets reinforced with cream or cholesterol. In their opinion, the neutral fats and phospholipids function as solvents for the much less soluble cholesterol. In biliary cirrhosis after long-standing obstructive jaundice, the elevation of the phospholipids has been thought to be the explanation for the lack of the atherogenic effect of the concurrent hypercholesterolemia (Ahrens, 1950). The same explanation is given for the lack of intensified atherogenesis following experimental administration of alloxan (Duff, Brechlin and Finkelstein, 1954) or detergents (Kellner, 1955; Hirsch and Kellner, 1956).

Interest has also centered on the mechanism of transport of lipid. Chylomicrons, particulate structures which are responsible for lactescence of hyperlipemic serum, are largely composed of neutral fat. They contain only 5 per cent or less of cholesterol (Katz and Stamler, 1953); hence, cannot be accorded the significance in atherogenesis that Moreton (1947) had postulated. Proteins, in the form of complex lipoproteins, comprise a much greater fraction of the plasma lipids (Havel *et al.*, 1955; Bragdon *et al.*, 1956). Electrical charge and differences in electrophoretic mobility, variations in density as determined by the ultracentrifuge, and chemical distinctions all show that there are two distinct groups, *viz.*, the alpha and beta lipoproteins (Anfinsen, 1955). Together these include about 90 per cent of the plasma cholesterol in addition to other lipids. The major compositional differences between the two are tabulated below (Surgenor, 1955).

The chief alterations in concentration of blood lipid are "reflected almost quantitatively in the amount of lipid in the beta lipoprotein compartment" (Surgenor, 1955). Accordingly, this fraction and its relationship to atherosclerosis (in the form of coronary heart disease) have been studied most intensively by Gofman and associates (1952) who have indicated that the beta lipoproteins are composed of a whole spectrum of substances identified by their rates of flotation when suspended in a solution of sodium chloride having a density of 1.063 and subjected to ultracentrifugation.

TABLE XIV-1

Composition and Properties of the Major Lipoproteins of Human Plasma (Surgenor, 1955)

	Lipoproteins	
	Alpha	Beta
Density and ultracentrifugal characterization	1.16 (high density)	1.032 (low density)
Per cent of plasma proteins	3	5
	Lipid in Gm. per 100 Gm. of lipoprotein	
Unesterified cholesterol	3.3	8.3
Cholesterol esters	15.0	39.1
Phospholipids	21.0	29.3
Total lipids	39.3	76.7
Protein moiety	60.	23.
Mole ratios		
Free cholesterol to total cholesterol	0.27	0.27
Cholesterol to phospholipid	1.3	2.1
Cholesterol to nitrogen	0.053	0.28

Elevated values of certain of these (Sf 0-12 and Sf 12-400) show a correlation with coronary heart disease that is higher than the correlation of increased cholesterol levels with coronary disease. However, other workers who have measured ultracentrifugal lipoproteins could not confirm their thesis (Cofman *et al.*, 1956). A clearing factor (Anfinson, 1955) seems to be important in the metabolic degradation of the lipoproteins of low density. Administration of its activator, heparin, retards the development of atherosclerotic lesions in rabbits fed cholesterol but has no influence on the rate of regression of lesions (Horlick and Duff, 1954). In man, heparin reduces the proportion of lipoproteins of high density (Engelberg *et al.*, 1956).

The alpha lipoproteins, on the other hand, show a striking constancy in level (Surgenor, 1955). The diminishing proportion of plasma cholesterol which they incorporate with age, coronary heart disease, and hypercholesterolemic states (Eder, 1955) seems to be entirely secondary to increased values of the beta fraction (Baker *et al.*, 1955). It has been found that estrogens and estrogenic substances have a potent influence in reducing the ratio of beta to alpha lipoprotein; androgens counteract this effect. Accordingly, it seems reasonable to attribute the observed predilection of clinical atherosclerotic disease for the male to the effect of his androgens upon plasma lipid (Russ *et al.*, 1951; Barr, 1953).

In chickens, Katz and his associates (1955) have shown that the variations in serum lipids induced by estrogens diminishes the atherogenic influence of cholesterol-enriched diets and actually appears to reverse established lesions in the coronary arteries. Further insight into the influence of the sex hormones is furnished by the comparative studies of Keys (1956). The predominance of males is greater when the total incidence of atherosclerotic disease is high. "Female sex hormones offer their greatest protection only in the face of such extraordinary atherogenic forces as are generated by the current mode of life of the most prosperous western society" (Keys, 1956). A rising incidence of coronary deaths among women in the United States (Lee and Thomas, 1956) indicates that estrogenic sub-

stances cannot neutralize the influence of other factors in atherogenesis.

Cortisone or ACTH produce hypercholesterolemia both in chickens (Katz *et al.*, 1955) and rabbits but retard atherogenesis presumably because of diminished endothelial permeability (Adlersberg *et al.*, 1954; Gordon *et al.*, 1954). Reference has already been made to hypothyroidism as a condition associated with hypercholesterolemia and predisposing to atherosclerosis. It is pertinent to note that hypothyroidism induced by thiouracil is a prerequisite (Steiner *et al.*, 1949) to induction of atherosclerosis in dogs and is one of the means of producing arterial lesions in rats (Wissler *et al.*, 1954).

Complications

Necrosis is one of the frequent complica-

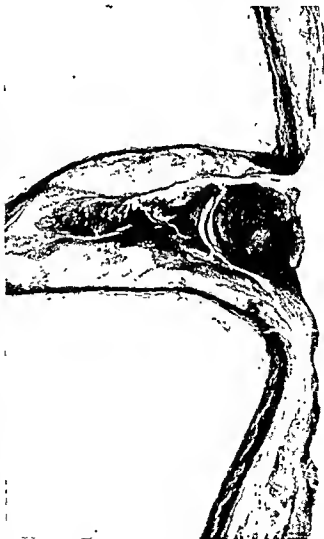


Figure XIV-4. Renal artery arising from aorta. The intima of both vessels is severely thickened by atheromatous deposits. The renal artery is occluded by a recent thrombus. X 4.

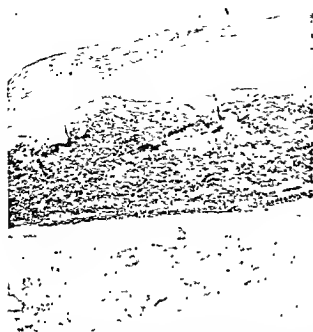


Figure XIV-5 Portion of aortic wall showing late effects of syphilitic infection. Note intimal sclerosis, focal areas of destruction of media, and thickened vasa and scarring in adventitia. The destruction of the elastic tissue in the media is responsible for weakening of the vessel wall. (AFIP, Accession 569786.) Orcein stain. X 10.

tions of atherosclerotic plaques. Ordinarily, it begins and may be limited to the base. With advanced disease it extends to involve the bulk of the lesion superficially and the contiguous portion of the underlying media; at times a narrow rim of muscle and elastic tissue may be all that remains of the aortic wall. The necrotic, grossly pasty and yellow-gray material, responsible for the name "atheroma," is acellular and palely acidophilic. It is rich in both amorphous and crystalline lipid and may contain granular deposits of calcium and a variable admixture of fresh or degenerating blood. A shaggy "atheromatous" ulceration may result from extension to and perforation of the thin superficial fibrous layer. On the other hand, dystrophic calcification of the superficial sclerotic layer may permanently seal the lesion. Formation of actual bone and marrow may result from ossification of the calcified plaque.

Thrombosis is a complication related to intimal roughening and to the tendency of atheromatous lesions to ulcerate (Figure

XIV-3). There is such an abundance of anastomotic circulation peripheral to the aorta that thrombotic occlusion of the ostia of the branches of the celiac axis or the superior or inferior mesenteric arteries usually causes no difficulty unless the collateral channels are already appreciably narrowed. Similarly, thrombotic occlusion of the orifice of one of the renal arteries (Figure XIV-4) may be symptomless. The possibility of correcting or eradicating aortic disease surgically has focused attention on the syndromes resulting from thrombotic obiteration of the aortic bifurcation, often termed the Leriche syndrome (Leriche, 1940; Leriche and Morel, 1948; Barnett *et al.*, 1952; Kekwick *et al.*, 1952; Beaconsfield and Kunlin, 1953; Burt *et al.*, 1952; Callow, 1954; Luke, 1954; DeBakey *et al.*, 1955; Haimovici and Escher, 1956; Brown *et al.*, 1957; Massarelli and Estes, 1957; Kramer *et al.*, 1958). This is an insidious process which is compatible for years with nearly normal life. It is more common among males of early middle life in whom impotency is one of the prominent symptoms. Other symptoms include easy fatigability of the lower limbs, "global" muscular wasting of the buttocks and lower limbs, coldness and sluggish wound-healing. Although Leriche emphasized the absence of intermittent claudication and trophic changes, these conditions may occur if the iliac and femoral arteries are involved (Burt *et al.*, 1952; Kekwick *et al.*, 1952; Callow, 1954; Brown *et al.*, 1957). Absence of femoral pulsation is a cardinal finding. The insidious onset of this form of occlusion clearly distinguishes it from sudden dramatic embolic occlusion.

Emboli originate most commonly from mural thrombi of the left side of the heart, but sometimes from proximally situated clots in the aorta; rare sources are valvular vegetations, fragments of a heart tumor and even foreign bodies introduced by trauma. The incidence of saddle embolism of the aorta (Albright and Leonard, 1950) ranges from 4 to 8 per cent of all arterial emboli.

The initial thrombosis is said to originate more frequently in one of the iliac arteries and involve the bifurcation by retrograde extension; less often the clot starts in the aorta

(Leriche and Morel, 1948; Beaconsfield and Kunlin, 1953). As a consequence of long-standing occlusion, however, both common iliac arteries become converted into solid cords and the periaortic tissues become thickened and fibrotic (Leriche and Morel, 1948). Rarely thrombotic occlusion has been reported to result from extrinsic pressure rather than from a primary vascular lesion (Burt *et al.*, 1952).

Although patients who have had thrombosis may live for years, they are semi-invalids and subject to the imminent hazard of thrombosis in the collateral channels and gangrene (Luke, 1954) or to ascending thrombotic occlusion of the renal arteries and uremia (Callow, 1954). In order to avoid these hazards the procedure recommended is thromboendarterectomy or resection and replacement by graft (DeBakey *et al.*, 1955).

Pertinent to a discussion of the Leriche syndrome, a few cases have been described with stenosis of the aorta distal to the arch. Kaufman and Markham (1955) reviewed 10 cases involving the thoracic, and 8 involving the abdominal aorta. The thoracic narrowing is generally diffuse

and elongate and its association with periaortic fibrosis suggests an acquired condition, such as an organized thrombus. Following Maycock (1937), Kaufman and Markham regarded coarctation of the abdominal aorta as congenital. In their case and in 2 of the remaining 7 there were associated defects or anomalies of the vascular system. The stenosis is localized to a point slightly above, at the level of, or just below the renal arteries. Morphologically there is no sharp distinction between congenital and acquired lesions. Ritchie and Douglas (1956) have described an example of atresia of the infrarenal segment of the aorta in which it would be reasonable to accept a congenital origin, were it not for the onset of progressive symptoms late in life.

Ectasia or diffuse dilatation is commonly related to atherosclerosis, but may occur without it (Barnett *et al.*, 1952). Accordingly, it represents an exaggeration of the elongation and dilatation which takes place with aging. It may be found in association with advanced cerebral atherosclerosis. In the cerebral vessels it is presumably related to the thinness of the media. In this location

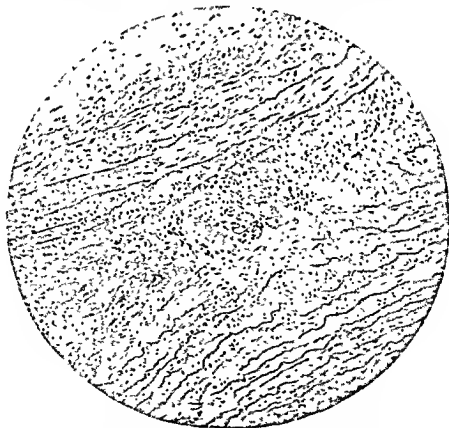


Figure XIV-6. Syphilitic aortitis. Note interruption of continuity of elastic lamellae and scarring in media. (WCGH, 32 A 115.)



Figure XIV-7. Syphilitic aortitis with granulomatous reaction and scarring. Hematoxylin and eosin. (WCGH, 46 A 437.)

it has little or no clinical importance. In the thoracic aorta its radiologic appearance may simulate that of a mediastinal tumor (Steinberg, 1956). Kinking of the elongate channel in the region of the ligamentum arteriosum, associated with a systolic basal murmur, simulates coarctation (Bruwer and Borchell, 1956). Angiocardiography, of course, clearly

delineates the true situation. In the abdomen, elongation of the aorta between the relatively fixed points of the diaphragm and the iliac bifurcation results in deviation ventrally and to the left.

Aneurysm, the third, and statistically, the most significant complication of atherosclerosis, is discussed on page 914.

2. INFLAMMATORY LESIONS OF AORTA

Syphilis

Syphilis is by far the most important cause of aortitis.

Clinical Features. Cardiovascular syphilis, essentially limited to disease of the aorta and the aortic valves, accounts for more than a third of fatal syphilis (Stokes *et al.*, 1945). It is two to four times as common in men as in women and about twice as frequent among Negroes as in white persons (Table XIV-2). Vascular dissemination of the causative treponeme occurs very early after infection, and

injury to the blood vessels is a fundamental lesion in the pathology of syphilis. However, clinical manifestations of aortic disease are generally delayed two to three decades and the peak incidence is between 35 and 55 years of age. Nevertheless in 10 per cent of 186 patients, syphilitic aortitis appeared less than 5 years after infection (Cole *et al.*, 1936). Cardiovascular syphilis accounts for 10 to 15 per cent of all heart disease presenting after age 50; but as autopsy experience discloses (Langer, 1926; Moore, 1943), this figure com-

TABLE XIV-2

Cardiovascular Involvement in Late or Latent Syphilis
(Cole *et al.*, 1936)

Late or latent syphilis	6253 (100%)
Cardiovascular syphilis	619 (9.9%)
(8 1% of white and 31 0% of colored males)	441 males
(6 1% of white and 12 8% of colored females)	178 females
Uncomplicated aortitis	4 9%
Aortic valvular insufficiency	4 1%
Aortitis and sacular aneurysm	1 2%
Syphilitic myocarditis	0 8%

Cardiovascular Syphilis (547 Cases)
(Rich and Webster, 1952)

Aortic insufficiency	309
Syphilitic aortitis	141
Aneurysm	95
Stenosis of coronary ostia	2

prises only that fraction of aortic syphilis in which the lesion has attained clinical magnitude,

The more obvious signs and symptoms of syphilitic aortic disease, unfortunately, are those of advanced disease. In aortitis the earliest physical sign is accentuation and tympanitic quality of the aortic second sound. An aortic systolic murmur may be present and there may be continuous substernal burning pain. Radiologically a

bulging of some part of the aortic arch is regarded as pathognomonic; the demonstration of calcification in the ascending arch is a helpful diagnostic finding (McCann and Porter, 1956). Serologic reactions are positive in 72 per cent, and remain positive in 52 per cent of patients who have received treatment (Cole *et al.*, 1936). Clinical manifestations and changes in the cerebrospinal fluid, indicating neural involvement, are present in 50 to 70 per cent of persons with cardiovascular syphilis. Diminishing cardiac reserve, paroxysmal nocturnal dyspnea and anginal attacks, occurring suddenly in a relatively young person, should arouse suspicion of syphilis. Progression of the anatomic changes leads to aortic regurgitation or aneurysm. Aortic insufficiency is characterized by a diastolic murmur, a collapsing pulse, capillary pulsation and cardiac enlargement.

Pathology. The *Treponema pallidum* invades the aortic wall by way of the vasa vasorum and since, according to Saphir and Scott (1927), the first portion of the aorta is most richly vascularized, disease of that segment is most frequent. As elsewhere, the infection produces endothelial swelling, hyperplasia and consequent occlusion of the vasa



Figure XIV-8. Syphilitic mesoaortitis with stellate granuloma. Note destruction of muscular and elastic fibers with scarring. van Gieson and orcein. (WCGII, 36 A 394.)



Figure XIV-9. Syphilitic aortitis, showing characteristic puckering of intima (WCGH, 36 A 419.)

so that ischemic necrosis contributes significantly to the destructive effects of the spirochetes in the media. Characteristically, the elastic and muscle fibers of the aortic wall are destroyed in a patchy or "moth-eaten" fashion (Figures XIV-5 and 6). Early, there is inflammatory thickening of the vessel wall and a mononuclear cellular infiltrate rich in epithelioid cells and plasma cells; occasional giant cells of the Langhans variety may be noted. The inflammatory reaction is most intense about foci of necrosis (Figure XIV-7) which may still show in "outline form" the structure of the unaffected tissue; being microscopic in size, the lesion is sometimes designated as a microgumma (Gordon *et al.*, 1942). The reparative response includes an influx of newly formed vasa from the adventitia, outlined by conspicuous collars of plasma cells and lymphocytes and narrowed by endothelial swelling and hyperplasia. With resorption of the necrotic debris, gaps in the musculoclastic lamina become filled with scar tissue which retracts, assuming a stellate shape (Figure XIV-8) and causing a corre-

sponding puckering of the overlying intima (Figure XIV-9). Accompanying the reparative process, there are marked fibrous thickening of the adventitia and sclerosis of the intima. Stokes and associates (1945) presented substantial clinical evidence pointing to the presence of mediastinitis with active inflammatory process in the aorta. Spirochetes are readily demonstrable in the acute active phase of syphilitic aortitis which is seldom seen, but are infrequent in the smoldering inflammatory lesion that is usually seen at autopsy. With cure of the infection, the inflammatory and degenerative changes resolve, leaving as vestiges acellular stellate fibrous scars in the media and fibrous thickening of both adventitia and intima.

With this background, the characteristic gross features of syphilitic aortitis are readily understood. Defects and scars in the media account for aortic dilatation and for the characteristic linear wrinkling of the intimal surface. To some extent, weakening of the media is compensated by fibrous thickening of the adventitia and intima which appreciably increases the thickness of the diseased wall. The smooth, pearly, intimal plaques so frequently observed are the gross counterpart of the intimal sclerosis seen microscopically. As they age, they are subject to deposition of lipid, accounting for the pathologic maxim that syphilitic aortitis augments the severity of atherosclerosis (Figure XIV-10). Because of that complication, calcium may frequently be

TABLE XIV-3

Incidence and Prognosis of Cardiovascular Syphilis (Moore, 1943)

Clinical Type	Per Cent of Late Syphilis Affected	Prognosis	
		Untreated	Adequately Treated
Subclinical aortitis	70-90	Good; no accurate data	Excellent
Uncomplicated aortitis	5-10	5-10 years	10-20 years or more
Saccular aneurysm	1-2	1-2 years	5-10 years
Aortic regurgitation	2-3	2-3 years	4-10 years
Myocarditis; coronary ostial stenosis	0.2-0.5	No accurate data	No accurate data

demonstrable radiologically in the ascending arch of syphilitic aortas (McCann and Porter, 1956; Lodwick and Gladstone, 1957). Intimal sclerosis overlying a diseased media is also responsible for syphilitic coronary ostial narrowing (Moritz, 1931).

The pathology of syphilitic aneurysms is discussed on page 915.

Rheumatic Aortitis

Klotz (1912) was the first to call attention to this process. According to Klinge and Vaubel (1931), involvement of the aorta is usual in acute rheumatic fever. Pappenheimer and Von Glahn (1924) and Klinge (1933) have characterized the gross lesion in the proximal aorta as elevated, translucent, intimal plaques of brown color. The histologic structure of the lesion is comparable to rheumatic involvement of the atrial endocardium, and consists of elongate foci of fibrinoid degeneration with surrounding cellular infiltrate rich in large, frequently multinucleated, basophilic histiocytes. Healing occurs by fibrosis, leading to nonspecific intimal scars. Frequently the aortitis is limited to the intima, but the process may extend deeper to involve both the media and adventitia. Klinge (1933) suggested that injury from the surface leads to the intimal lesion whereas the vasa vasorum carry the process to the outer coats. Microscopically, these layers present edema, vascularization, and a diffuse as well as perivascular cellular infiltrate. Foci of fibrinoid necrosis may be found in the adventitia, lying in relation to accumulations of large basophilic histiocytes. Thickening of the aortic wall, which may be noted in chronic rheumatic heart disease (Klotz, 1912), represents the nonspecific healed fibrotic stage of the process. Distinction from syphilis is generally based on lesser destructiveness of rheumatic aortitis, absence of medial gummatous necrosis and presence of fibrinoid necrosis (Pappenheimer and Von Glahn, 1926). Sometimes, however, rheumatic vascular lesions may be quite destructive (Gross, 1935).

Rheumatoid Aortitis

In 1951, Baer and associates reported that

rheumatoid arthritis may be associated with aortitis and an aortic endocarditis which clinically and anatomically resembles the lesion produced by syphilis.

Of 600 rheumatoid patients seen at the Massachusetts General Hospital during the course of 18 years, 19 patients presented this syndrome but had no evidence of mitral stenosis. In all of them, the arthritic process had involved the spine.

On the basis of their findings in 7 autopsies, Clark and co-workers (1957) described pink-red, coarsely granular, pannuslike intimal plaques or pearly gray, smooth scars with shell-like calcifications centering about the commissures and extending into the aortic sinuses and the first 2 to 3 cm. of the aorta. In 2 cases the coronary ostia were distorted, and in one case the left coronary artery had a small saccular aneurysm, 1 cm. in diameter, at its origin. The involved segment presented scarring of the adventitia, the cusps of the aortic valve were shortened and thickened and their free margins were rolled, the cusps being separated by widened commissures (Figure XIV-11). Evidence of functional in-

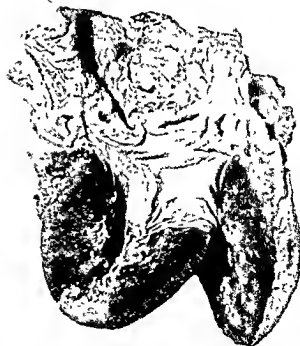


Figure XIV-10. Syphilitic aortitis with severe superimposed atherosclerosis. Syphilitic aortic insufficiency. Note dilatation of ascending aorta and separation of cusps at commissures. (WCGH, 45 A 351.)



Figure XIV-11 Rheumatoid aortitis with involvement of aortic valve, aortic sinuses, and first 2 to 3 cm of aorta, from patient with rheumatoid spondylitis. Note intimal thickening, commissural widening, and eversion and foreshortening of the valve cusps. (Courtesy of Dr. J. P. Kulka, Harvard Medical School.)

sufficiency was found in hypertrophy and dilatation of the left ventricle; and in sub-aortic endocardial pockets in three cases. Microscopically, within the media active lesions were characterized by foci of necrosis and vascular granulation tissue, and by perivascular accumulations of lymphocytes and plasma cells. In the corresponding area, the intima was thickened by an overgrowth of mucinous connective tissue with little or no inflammation, and the adventitia was thickened and fibrous and contained prominent vasa outlined by perivascular accumulations of inflammatory cells.

Primary Acute Aortitis

Primary acute aortitis is an exceedingly rare condition in which the inflammatory process in the aorta cannot be related either to endocarditis or to inflammation in an adjoining structure.

von Stumpf (1913) reported a case and was able to find only 9 other recorded instances. Rappaport (1926) described suppurative infection of the intima of the supra-avalvular segment of the aorta caused by gram-positive diplococci. It was presumed that underlying syphilitic aortitis

had contributed to this localization. Saphir and Cooper (1927) reported a similar occurrence. In the case described by Williams (1952), its association with medial degeneration resulted in dissecting aneurysm.

Martin and associates (1955) have emphasized the vulnerability to infection of the "jet lesion," the intimal plaque distal to the aortic coarctation resulting from the impact of the blood stream. Indeed, in this congenital lesion, subacute bacterial endarteritis is a major hazard (Abbott, 1928; Reifenshtein *et al.*, 1947; Edwards *et al.*, 1948).

Tuberculous Aortitis

Tuberculous infections of the aorta have been reported in 23 instances (Scott *et al.*, 1949; German and Green, 1956). In all except two, the infection had spread directly to the aortic wall from a para-aortic focus. In most instances, also, weakening of the vessel wall resulted in the formation of an aneurysm. (See section on mycotic aneurysms.)

Giant-Cell Aortitis

In 1937, Sproul and Hawthorne, under the designation *chronic diffuse mesaortitis*, re-

ported 2 instances of a lesion characterized by destructive inflammation of the elastic and muscle laminae and the presence of Langhans giant cells. Similar histologic features are to be found in temporal arteritis (Kimmelstiel *et al.*, 1952) and accumulated experience (Harrison, 1948) has made it clear that these are but differing anatomic manifestations of a widespread vascular disease. Giant cells and granulomatous inflammatory reactions (Figure XIV-12) are so conspicuous that the designation *giant-cell arteritis* is now used almost uniformly (Gilmour, 1941; Harrison, 1948, Kimmelstiel *et al.*, 1952).

As summarized by Harrison (1948), the disease involves older persons of either sex. The clinical course of several months' duration, is characterized by malaise, fever, anemia, leukocytosis and increased rate of sedimentation of erythrocytes. Clinically, the patients present prominent, thickened and painful, temporal arteries. Blindness and cerebral disturbances are not infrequent complications and indicate involvement of other cranial arteries. Most patients recover, and relief is obtained by use of cortisone or ACTH (Harrison *et al.*, 1955). At the time of Harrison's review in 1948, there were reports of 16 autopsy cases, characteristic lesions were

found in the aorta (9 cases), carotid arteries (6), iliac arteries (4), mesenteric and subclavian arteries (3 each), innominate and femoral arteries (2 each), and in the pulmonary, coronary, celiac, renal, radial and retinal arteries (1 case each). Aortic involvement was more common in the 13 autopsies reported since 1948 (Magarey, 1950, one case; McMillan, 1950, one, Cardell and Hanley, 1951, one; Frangenheim, 1951, one; Ritama, 1951, one, Meneely and Bigelow, 1953, one; Heptinstall *et al.*, 1954, 3 cases, Gelfand, 1955, one; Lander and Bonnin, 1956, one, and Brody and Krasnoff, 1956, 2 cases). These cases included an aneurysm of the diseased aortic arch in a 2-year-old African boy (Gelfand, 1955) and 4 dissecting aneurysms (Magarey, 1950; McMillan, 1950, Brody and Krasnoff, 1956, 2 cases).

Intimal thickening by fibrosis and accumulation of interstitial mucoid material is conspicuous in involved temporal arteries and results in considerable luminal narrowing (Harrison, 1948). In the aorta, however, the disease is largely confined to the media. Macroscopic changes are usually not seen, though Sproul and Hawthorne (1937) and Gelfand (1955) had observed longitudinal intimal wrinkling, and there may be superficial deposits of fibrin. Microscopically the media, which bears the



Figure XIV-12. Giant-cell arteritis. Note inflammatory thickening of the intima, giant-cell reaction at site of disintegrating elastic intima, and engulfment by giant cells of short segments of elastic tissue.



Figure XIV-13 A and B. Syphilitic aneurysm of descending portion of thoracic aorta, causing erosion of ventral portions of bodies of dorsal vertebrae. From a man of 43. (WCGH, 36 A 418.)

brunt of the damage, is diffusely infiltrated with lymphocytes, macrophages and plasma cells, with resulting destruction and disappearance of muscle and focal disruption and fragmentation of the elastic laminae. Foreign-body giant cells lie in relation to fragments of degenerating elastic tissue (Kimmelstiel *et al.*, 1952), although it may be necessary to examine several levels to demonstrate them (Harrison, 1948). Damage to the elastica interna, in smaller arteries at least, distinguishes the lesion from thromboangiitis obliterans. Increased vascularization of the media occurs as part of the inflammatory reaction. Changes in the aortic adventitia are slight or absent, in contrast to the striking adventitial fibrosis in involved temporal arteries. The etiology is unknown. The clinical behavior suggests infection but no organisms have been demonstrated.

Pulseless Disease

There is considerable interest in an uncommon condition characterized by absence of the radial pulses, called "pulseless disease."

Attention was first drawn to the syndrome in 1908 by the Japanese ophthalmologist, Takayasu (cited by Caccamise and Whitman, 1952), to whom it was apparent that the lesion involved obliteration or occlusive changes in the vessels arising from the aortic arch (Frovig and Loken, 1951; Slipper and Flint, 1952). Caccamise and Whitman were able to find reports of 58 cases up to 1952, most of them in young Japanese females. The condition, however, is more widespread geographically, and by 1958 more than 100 cases had been reported (Moia *et al.*, 1956; Birke *et al.*, 1957; Kalmansahn and Kalmansahn, 1957; Ollendorf, 1957). The syndrome is chronic and progressive and has a poor prognosis. In addition to absence or diminution of pulsation in the ar-

tenes to the head, neck and upper extremities, the patient may have weakness and easy fatigability of the arms, reduced visual acuity, and dizziness or syncope upon assuming the erect position. Ocular and cerebral disturbances are often disabling and permanent (Ask-Upmark, 1954) and death may result from the neurologic disorder.

Pathologically, the aortic arch and the arteries arising from it present a panarteritis involving all layers of the arterial wall and ultimately producing obliteration by centralization or thrombosis or both (Ask-Upmark, 1954; Bustamente *et al.*, 1954; Ask-Upmark and Fajers, 1956). Barker and Edwards (1955) described and illustrated extensive infiltration of the media by lymphocytes and macrophages, some increase in vascularization and "nonatheromatous" intimal thickening which, in their case, had narrowed the coronary ostia. In the case reported by Frovig and Loken (1951), giant cells were present in the infiltrate, and therefore it was suggested that the condition may be related to

temporal or giant-cell arteritis (Ask-Upmark and Fajers, 1956; Boccacelli, 1955). The absence of pulsation in the upper part of the body, its presence in the lower, and the prominence of collateral channels led to the term "reversed coarctation" for the syndrome (Weir and Kyle, 1956), but this term is a poor one since the condition is acquired and coarctation implies a congenital origin. Ross and McKusick (1953) and Kalmansahn and Kalmansahn (1957) have indicated that the etiology is varied and that syphilis, atherosclerosis, chronic dissecting aneurysm, and trauma may at times be responsible for the occlusive syndrome of the aortic arch. Even if these entities can be excluded, the varied histologic appearance of different cases, like those of Barker and Edwards (1955) and Frovig and Loken (1951), suggests different etiologies. Both anticoagulant therapy and thromboendarterectomy (Spittel and Siekert, 1957; DeBaKey *et al.*, 1958) have been recommended.

3. AORTIC ANEURYSMS

Any abnormal localized dilatation or widening of the aorta constitutes an aneurysm. In appearance it may be saccular, communicating with the arterial channel through a relatively narrow neck, or fusiform, in which case the involvement of the wall of the vessel is more diffuse, usually producing a spindle-shaped but sometimes a globular out-pouching. Dissecting aneurysms usually communicate with the lumen through one or more tears or rents in the intima; exceptions, consisting of strictly intramural hemorrhages, are of importance only because they provide insight into their pathogenesis (Core, 1952). Of 412 aneurysms, Brindley and Stenbridge (1956) classified 59.5 per cent as saccular, 27.7 per cent as fusiform and 10.7 per cent as dissecting.

All aneurysms result from structural weakening of the vessel wall. The major processes contributing to them are syphilis, atherosclerosis, idiopathic medial degeneration, infections, trauma and congenital defects. The

over-all necropsy incidence, which has diminished moderately in the past few decades, varies from 2 to 4 per cent (Brindley and Stenbridge, 1956). Exclusive of dissecting aneurysms, a summary of 9 separate investi-

TABLE XIV-4
Location, Etiology and Age in 412 Cases
of Aortic Aneurysm
(Brindley and Stenbridge, 1956)

	First 100 Cases 1892-1928	Last 100 Cases 1943-1953
Incidence at necropsy	4.36%	3.43%
Location		
Thoracic	82	68
Abdominal	13	22
Thoraco-abdominal	5	10
Etiology		
Syphilis	77	49
Atherosclerosis	9	27
Medial degeneration (dissecting)	1	22
Other	13	2
Age (average)		
Over-all	46.2 years	61.8 years
Syphilitic	44.8	61.0
Atherosclerotic	71.0	65.5



Figure XIV-14 Erosion of ventral portions of bodies of dorsal vertebrae by syphilitic aneurysm. Note that the intervertebral disks were more resistant than the spongy bone to the erosive effect of the aneurysm. From a man of 81. (WCGH, 36 A 419)

gations (Cranley *et al.*, 1954) indicates an incidence of 1.5 per cent. Over the past few decades syphilis has become less dominant as a cause of aneurysm, and mycotic forms less frequent, both atherosclerotic and dissecting aneurysms have become increasingly common as indicated in Table XIV-4.

Syphilitic Aneurysms

Clinical Features. Aneurysms produce a systolic bruit, diastolic shock, and an abnormal mass which may be detected by physical or x-ray examination. The suggestion has been made that the occurrence of aortic insufficiency protects, to some degree, against subsequent development of an aneurysm (Stokes *et al.*, 1945). The symptoms and signs produced by aneurysms depend upon their location and the effects of their pressure on surrounding structures. The great majority of syphilitic aneurysms involve the thoracic aorta and principally the arch (Table XIV-5). In one

large series, aneurysmal involvement of the thoracic aorta was limited to the ascending portion or the arch in 91 per cent (Cranley *et al.*, 1954). With the onset of symptoms in syphilitic aneurysm, life expectancy is poor. Cranley and associates found that 59 per cent of patients with syphilitic aneurysm died within one year and 77 per cent in less than 2 years. Patients with abdominal aneurysms develop symptoms late and have a much shorter interval of survival. Death was related to rupture and hemorrhage in 59 per cent and to compression and erosion of vital structures in 39 per cent. Even after rupture there is the possibility of salvage since 25 per cent of persons with ruptured syphilitic aneurysms live longer than 6 hours. Some effects of aneurysms of the aortic arch include: difference in blood pressure in the two arms; hoarseness resulting from pressure on the recurrent laryngeal nerve; inequality in size of pupils, resulting from involvement of sympathetic nerves; and tracheal tug or compression. The introduction of aortography has greatly helped in distinguishing aneurysm from tumor. Syphilitic aortitis seems to be one of the principal causes of the uncommon disorder, "pulseless disease" (Ross and McKusick, 1953). In this condition a productive arteritis results in obstruction of the brachiocephalic vessels at or near their origin from the aortic arch (Weir and Kyle, 1956). In a small proportion of cases, signs and symptoms of coronary sclerosis result from extension of the aortitis to the coro-

TABLE XIV-5

Incidence of Race and Sex, and Anatomic Location in 189 Syphilitic Aortic Aneurysms (Cranley *et al.*, 1954)

Incidence		
Negro	120 (64%)	
Male		95 (79%)
Female		25 (21%)
White	69 (36%)	
Male		58 (84%)
Female		11 (16%)
Location		
Thoracic aorta	169 (89%)	
Ascending		32
Ascending and arch		28
Arch		50
Arch and descending		22
Descending		14
Unspecified		3
Abdominal aorta	20 (11%)	
Proximal to renal arteries		18
Distal to renal arteries		2

TABLE XIV-6

Etiology and Location of 365 Aortic Aneurysms
(Blakemore and Voorhees, 1954)

Etiology	Thoracic Aorta	Abdominal Aorta
Atherosclerosis	29	114
Syphilis	182	10
Miscellaneous	15	13

nary ostia and at times along the proximal segment of the vessels (Moritz, 1931). About one fifth of patients with syphilitic aortitis have coronary ostial involvement (Burch and Winsor, 1942, Montgomery *et al.*, 1952) and the incidence of myocardial infarction is several times as great (Burch and Winsor). The importance of early diagnosis and treatment is apparent from Table XIV-3 and from the study of Rich and Webster (1952).

Pathology. Medial weakening may be extensive enough in a given area to cause aneurysmal bulging of the aortic wall under the thrust of the blood stream (Figures XIV-13-17). Most syphilitic aneurysms are saccular (Kampmeier, 1938). Their walls are fibrous with no recognizable medial constituents except at their ostia. Even relatively small aneurysms become filled with laminated thrombus, the most recent layers of which are adjacent to the wall of the sac. Doubtless the thrombus is intended to protect the wall from the hemodynamic force but the latter continues to expand with the sac with each pulsation, thus preventing organization of the aneurysmal thrombus and leading to accretion of additional clot (Figure XIV-18). Although pressure of the blood is instrumental in producing aneurysms, hypertension is not more prevalent among those affected. Victims of aortic regurgitation are less likely to develop aneurysms but are more likely to develop myocardial failure as a result of narrowing or atresia of the coronary orifices, coronary sclerosis and ultimate decompensation of a hypertrophied but inadequate myocardium (Stokes *et al.*, 1945).

Atherosclerotic Aneurysms

The great majority of atherosclerotic aneurysms are located in the abdominal aorta (Table XIV-6).

Clinical Features. The aneurysms represent complications of severe atherosclerosis and comprise a large and increasing proportion of aortic aneurysms (Maniglia and Gregory, 1952, Blakemore and Voorhees, 1954; Parkhurst and Decker, 1955; Brindley and Stenbridge, 1956). They are more frequent among men and among older persons. Two thirds of the 44 aneurysms of Crane's (1955) were from patients in the sixth and seventh decades.

Within the abdominal aorta, syphilitic aneurysms tend to localize above the renal arteries (Kampmeier, 1936, Cranley *et al.*, 1954), whereas most atherosclerotic aneurysms occur below that level (Blakemore, 1947; Wheelock and Shaw, 1956). Not uncommonly atherosclerotic aneurysms are multiple (Parkhurst and Decker, 1955).

Estes (1950) found a long asymptomatic course in 30.4 per cent (102 patients). In 86 per cent of cases lateral x-ray films of the abdomen disclosed a large oval or spheroid mass of soft tissue with scattered calcified curvilinear,



Figure XIV-15. Lateral view of patient 6 weeks prior to death from external rupture of syphilitic aortic aneurysm. (WCGH, 47 A 178.)



Figure XIV-16. Ventral view of patient at necropsy, following external rupture of syphilitic aortic aneurysm. (WCGH, 47 A 178.)

linear or laminated plaques (Petersen, 1952). In general, atherosclerotic aneurysms enlarge and ultimately lead either to thrombosis or rupture. Symptoms result from pressure and adjacent inflammatory reaction and include abdominal or lumbar pain, varying in nature from dull and steady to severe and pulsating, which may be referred to the testis or thigh. An abdominal mass is generally easy to identify when the aneurysm exceeds 5 or 6 cm. in diameter. After a variable interval, rupture supervenes. Among 102 patients in Estes' series, rupture caused death in 63 per cent. In one third, death occurred within a year, and in two thirds within 3½ years; only 19 per cent survived 5 years and none of the patients lived longer than 8 years. Kampmeier (1936) reported that 82 per cent of patients died within 6 months, presumably because more of them had advanced disease. Pathologic findings (Cranley *et al.*, 1954) make it clear that many atherosclerotic aneurysms are unrecognized during life since in 75 per cent of patients the aneurysm had no relationship to the patient's death.

The likelihood of rupture increases with the size of the aneurysm (Crane, 1955; Shapiro, 1957). Crane (1955) found that only one of 26 aneurysms less than 6 cm. in diameter had ruptured, in contrast to 14 of 17 which were larger than 7 cm. Mural thrombosis is almost invariably present (Blakemore, 1947) and probably is a factor in slowing the escape of blood from the rup-

ture and preventing prompt death. Blakemore estimated that there is generally an interval of 2 to 6 days between the initiation of retroperitoneal hemorrhage and death. Rarely there is massive escape of blood into the abdominal cavity (Blakemore, 1947; Copping, 1953), and exceptionally, prolonged and slow leakage may produce a massive organized fibrotic mass simulating a retroperitoneal tumor (Betts and Rowland, 1953). Distal embolization from the contents of a thrombosed aneurysm is rare (Wheelock and Shaw, 1956), presumably because the most recent clot lies adjacent to the wall and not adjacent to the rapidly flowing axial stream.

From the viewpoint of prospective surgical intervention, an atherosclerotic aortic aneurysm signifies the presence of generalized atherosclerosis; however, there is no uniformity in the severity of the atherosclerosis. Of 21 patients with abdominal aneurysm, Wheelock and Shaw (1956) found that only 8 had clinical evidence of coronary heart disease and only 6, of peripheral arterial insufficiency. Pathologically, among 44 patients Crane (1955) demonstrated recent occlusive coronary artery disease in 14 and cerebrovascular lesions in 2. The incidence of hypertension (24 of 39 patients) in his series, does not seem more than would be expected among middle-aged and old persons.

Pathology. Atherosclerotic aneurysms vary

from spindle to globular shape. All of them communicate widely and freely with the axial stream and, by definition, are fusiform aneurysms. However, there is an erroneous tendency to classify globular lesions as saccular (Cranley *et al.*, 1954). As indicated elsewhere, these aneurysms arise because of the effects of severe intimal atherosclerosis upon the adjacent media. Attenuation and destruction of this layer with replacement by fibrous tissue results in loss of the property of elastic recoil. Under the impact of the pulse, the vessel dilates and the weak and deficient wall of the expanded channel is subjected to increased tension in accordance with the principle of Laplace (De Takats and Pirani, 1954). As the rate of flow diminishes with dilatation, the lateral hydrostatic pressure increases. Mural thrombosis takes place in the great majority of abdominal aneurysms (Blakemore, 1947). The pulsation of the inelastic wall of the sac leads to detachment of the thrombus and a new clot forms beneath the old. Repetition of the process results in a laminated thrombus with the newest accretion at the periphery, but this does not become organized because the clot does not adhere. Generally, a channel persists through or to one side of the thrombus, complete thrombotic occlusion is unusual with aortic aneurysms although it is not uncommon in aneurysms of the peripheral arteries. As mentioned, the thrombus and the fibrosis of the wall of the sac serve to delay but not to prevent expansion or rupture of the aneurysm. Surgical duplication of these natural measures by wiring and electrocoagulation (Blakemore, 1951), or by wrapping or reinforcement have been largely superseded by excision and insertion of homografts or plastic prostheses (DeBakey and Cooley, 1953; Farrar *et al.*, 1956; Roberts *et al.*, 1957).

Dissecting Aneurysms

In dissecting aneurysms, in contrast to other forms, deformity of the vessel results from hemorrhage which splits the media and extends for a variable distance along the length of the channel. This lesion is largely restricted to the aorta, though it has been reported as

a rare event in coronary (Glendy *et al.*, 1937), cerebral (Bigelow, 1955), superior mesenteric (Bauersfeld, 1947), and renal arteries (Gore, 1953).

Historically the first unmistakable description was Nicholls' (1761) account of an "incipient" unruptured aneurysm in King George II (Shennan, 1934; Burchell, 1955). Sherkelton (1822) gave an account of the chronic form of the disease with rechannelization, but the designation *dissecting aneurysm* was first introduced in 1826 by Laennec. Elliotson's (1830) presentation in 1829 would do credit to a present-day text, and by 1863

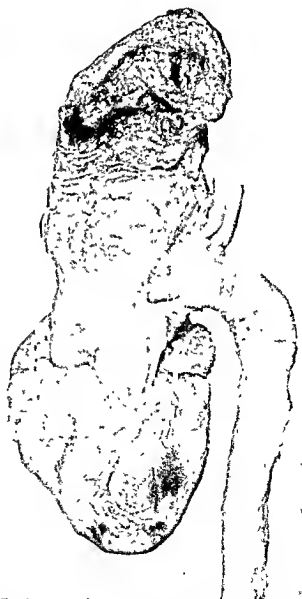


Figure XIV-17. Ventral view of heart and aorta with rupture of syphilitic aneurysm of transverse portion of arch. From patient shown in Figures XIV-15 and XIV-16.



Figure XIV-18 Syphilitic aneurysm of transverse portion of arch of aorta, showing lamination of blood clot in aneurysmal sac. From a man of 49. (WCGH, 36 A 38)

Peacock was able to marshal 80 cases for review.

Clinical Features. The most dramatic of the aneurysms in onset, progression and varied manifestations, it is being diagnosed with increasing frequency (Bauersfeld, 1947; David *et al.*, 1947; Baer and Coldburgh, 1948; Warren and McQuown, 1948; Levinson *et al.*, 1950; Core and Seiwert, 1952; Baer, 1956; Hirst *et al.*, 1956). Like atherosclerotic aneurysms, it comprises a growing proportion of all aortic aneurysms, having an incidence estimated at 12 to 25 per cent (Maniglia and Gregory, 1952; Cranley *et al.*, 1954; Parkhurst and Decker, 1955; Brindley and Stembidge, 1956). No age group is exempt, but three fourths of the patients in more than 500 collected cases (Hirst *et al.*, 1956) ranged in age from 40 to 70 years (Figure XIV-19). Men are affected 2 to 3 times as often as women (Moersch and Sayre, 1950; Baer, 1956). There is no apparent racial predilection, if variations in the incidence of hypertension are considered (Levinson *et al.*, 1950).

Symptomatically the lesion is characterized by sudden onset of intense ripping, sharp or choking pain which resists sedation. The pain may persist

or subside, but its recurrence is an ominous symptom. Most often the pain is substernal or precordial but may be located at other sites, including the neck, epigastrium and shoulders. Migration or radiation of pain along the aorta is a highly suggestive symptom, especially if it occurs early in the course, in contrast to embolism complicating myocardial infarction. Abdominal pain may be associated with nausea, vomiting, hematemesis and melena; demonstration of tenderness and rigidity may then suggest the diagnosis. Rarely, it is possible to demonstrate an abdominal mass or ecchymosis (Moersch and Sayre, 1950; Burchell, 1955; Hirst *et al.*, 1950). Other symptom-complexes may simulate coronary thrombosis, cerebral vascular thrombosis or hemorrhage, hypertensive encephalopathy, pulmonary disease or transverse myelitis (Moersch and Sayre, 1950; Burchell, 1955; Baer, 1956).

Although the majority of victims of dissecting aneurysm succumb rather rapidly, there is usually adequate time for surgical intervention (DeBakey *et al.*, 1955 if clinical diagnosis is not delayed. Hirst and his associates tabulated the survival time in 425 cases collected from the literature

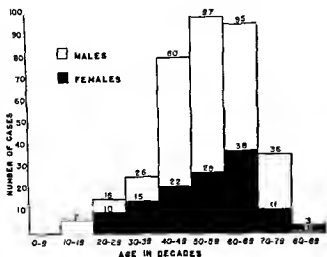


Figure XIV-19. Age and sex incidence among 485 patients with dissecting aneurysm of aorta, compiled from published reports. (Courtesy of Dr A. E. Hirst, Jr., Los Angeles.)

(Figure XIV-20) and found that 79 per cent of patients lived more than 24 hours, 51 per cent more than 4 days, and 26 per cent more than 2 weeks. Only 3 per cent of deaths were described as sudden. On the other hand, prolonged survival is possible and the recorded cases include survivals of 9 years (Cassidy and Pinniger, 1946), 15 years (Hall, 1926), and 30 years (Morgan-Jones and Langley, 1946); in 16 of 300 cases collected by Shennan (1934) the patient survived for more than one year.

External rupture of the aneurysm with hemorrhage is the cause of death in 95 per cent of those who do not survive for more than a few days (Shennan, 1934). Among 206 acute cases reviewed by Shennan, hemorrhage took place into the pericardial cavity in 152, into the pleural cavity in 30, into the mediastinal in 7 and into the lung in one. The importance of a tear of re-entry has been stressed in reducing the incidence of external rupture to 42 per cent (39 of 92 cases) (Shennan, 1934; DeBakey *et al.*, 1955), and in improving the chances of prolonged survival. (See Table XIV-7 prepared by Morgan-Jones and Langley (1946) from Shennan's data.)

Cardiac failure (Shennan, 1934; DeBakey *et al.*, 1955) and hemorrhage from the aneurysm are the most frequent causes of death in chronic dissecting aneurysm, the former occurring in 31 and the latter in 16 of 79 cases. Fatal hemorrhage in chronic lesions

results either from rupture of the original lesion or from additional or even multiple independent episodes of dissection (Gore and Seiwert, 1952; Bellomy, 1956; Prior *et al.*, 1957).

Gross Pathology. Most commonly an intimal tear in the ascending portion or arch of the aorta communicates with and contributes to a hemorrhage which has split the media into a thick inner and a thin outer portion.

The longitudinal extent of cleavage is variable. In so-called "spontaneous" rupture there is no appreciable linear dissection but in other respects it cannot be distinguished from more classical examples of dissecting aneurysm (Sailer, 1942; Gore and Seiwert, 1952). Externally, the intramural process deforms the aorta to a variable extent and produces either saccular or fusiform bulging. Frequently the false channel may bulge internally and encroach upon the natural one (Figure XIV-21). Once dissection has started, it usually extends distally, but some degree of retrograde dissection is common, particularly with prolonged survival (Shennan, 1934; Gore and Seiwert, 1952). As indicated in Table XIV-9, almost one-half of the dissections are limited to the ascending aorta and some segment of the aortic arch and 40 per cent extend to involve the thoracic or abdominal aorta. In 10 per cent the aneurysm takes origin in the transverse or distal aortic arch and frequently involves the abdominal aorta. The vessels of the lower extremities were involved in 19 of 85 cases. Comparable figures have been reported in other series (McGeachy and Paullin, 1937; Bauersfeld, 1947; Burehell, 1955).

Although more than half of the dissections involve the abdominal aorta, it is noteworthy

TABLE XIV-7

Effect of Tear of Re-entry of Period on Survival in 291 Dissecting Aneurysms

	Number of Cases	Survival for Less Than 5 Weeks	Survival for More Than 5 Weeks
No re-entry	199	192 (96%)	7 (4%)
Re-entry	92	26 (28%)	66 (72%)

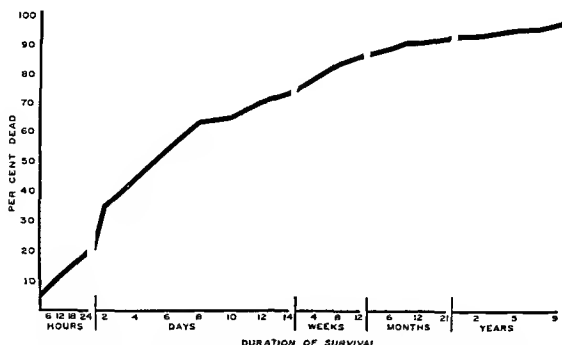


Figure XIV-20. Length of survival in 425 patients with dissecting aneurysm of aorta, compiled from published reports. (Courtesy of Dr. A. E. Hirst, Jr., Los Angeles.)

that of those that terminate with fatal hemorrhage (67 of 69) the great majority are intrathoracic (Figures XIV-22 and XIV-23). As already mentioned these involve the pericardium most frequently, the mediastinum or the pleural cavity. Rupture and external hemorrhage did not occur in 16 of the 85 cases reviewed; since only 4 of these patients died in less than 2 weeks, these patients fall in the group that might be benefited by surgery. This is also the group in which spontaneous internal rupture and rechannelization are likely to occur; 4 such cases with prolonged survival were encountered among the 85 reviewed. As previously mentioned, even with

old rechannelized dissecting aneurysms, termination from hemorrhage is frequent, as occurred in 7 of 11 patients (Gore and Selwert, 1952). A dissection within an aorta demonstrates the presence of disease and it is not at all astonishing that survivors of one episode should suffer one or more recurrences, terminating usually with a fatal episode of intramural hemorrhage. Tears of re-entry are important in re-establishing circulation and allowing decompression of the false channel. However, in this regard, inadequate emphasis

TABLE XIV-8

Anatomic Site of Intimal Tear in 85 Cases of Dissecting Aortic Aneurysm (Gore and Selwert, 1952)

Location	Cases	
	Number	Per Cent
Ascending aorta	53	63
Transverse aortic arch	15	18
Distal aortic arch	8	10
Thoracic aorta	6	7
Abdominal aorta (including one case affecting renal artery)	2	2
Totals	84*	100

*Two tears were present in each of 5 cases; in 6 cases there was no intimal defect.

TABLE XIV-9
Location and Extent of Intramural Dissection in 85 Dissecting Aneurysms

Location and Extension	Cases	
	Number	Per Cent
Ascending aorta	10	12
Only	10	12
And transverse aorta	16	19
And distal arch of aorta	4	5
And thoracic aorta	4	5
And abdominal aorta	30	35
Transverse aorta, distal arch, thoracic and abdominal aorta	8	9
Distal aortic arch and thoracic aorta	2	2
And abdominal aorta	4	5
Thoracic aorta		
Only	1	1
And abdominal aorta	4	5
Abdominal aorta	2	2
Totals	85	100

has been given to the similar effect of intramural splitting of subsidiary arteries by the dissecting process. Depending upon the pressure relations, the natural ostia of such intercepted vessels permit return of blood to the normal lumen and prevent the build-up of a significant differential of pressure. Moreover, the distal openings, now coming off the false channel, decompress it by providing the circulation to the involved arteries. Moersch and Sayre (1950) have indicated that transient cord symptoms may be explained by compression and attenuation of intercepted segmental channels before they are severed within the wall of the aorta. The same process affecting the renal arteries may well contribute to the very high blood pressure often observed during the acute illness (Burchell, 1955).

Much emphasis has been placed upon transverse orientation of the primary intimal laceration as a clue to the mechanical factors involved in the genesis of dissecting aneurysms. However, there are frequent exceptions (Burchell, 1955); particularly among victims in the younger age groups (Gore, 1953). Accordingly, it seems reasonable to infer that mechanical influences are subordinate to, and only assume significance in the face of, more fundamental changes within the vessel wall. In chronic forms of dissecting aneurysms, the intimal opening is round or ovoid and the edges are smooth and endothelialized. With time, the lining of the false channel also becomes endothelialized and has been found to be subject to atheromatous deposits and plaques (Weiss *et al.*, 1940; Cassidy and Pinniger, 1946).

Two variants of dissecting aneurysm merit consideration out of proportion to their frequency. Since the descriptions of Krukenberg (1920) and Tyson (1931), a number of cases of dissecting aneurysm have been reported without intimal tears (Figure XIV-24). In the study of 85 cases (Gore and Seiwert, 1952) tabulated above, there were 6 such instances and 17 others were listed from the literature. Additional examples have since been recorded (Levinson *et al.*, 1950; Jackson and Slavin, 1953; Hirst and Barbour, 1953),

and a more complete survey (Hirst *et al.*, 1956) suggests a frequency of about 10 per cent. Its importance lies in demonstrating that the usual intimal tear is, in all likelihood, a secondary event in the genesis of aortic dissection. Hirst and Barbour (1958) have described healing of an intramural dissection. The second even less frequent variant, *incomplete rupture of the aorta*, originally described (as a healed rupture) by Eppinger in 1887, has since been more fully documented (Peery, 1942; Fisher and Salmons, 1950). Characteristically the lesion, a non-penetrating rent in the intima and media, lies in the supralvalvular segment of the ascending aorta and is usually transversely oriented. A few tenuous strands sometimes bridge the gap between the edges of the torn intima. With survival, there is endothelialization of the base of the tear and reactive fibrosis of the subjacent adventitia. However, survival is limited by the propensity to dissection and rupture into the pericardium, as well as by



Figure XIV-21. Transection of aorta showing narrowing of lumen caused by a large hematoma splitting outer layers of the media. The atherosclerotic intimal disease is coincidental.

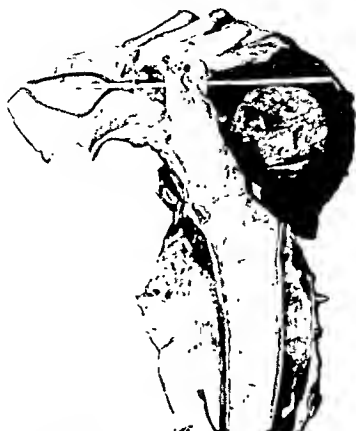


Figure XIV-22. Unruptured chronic dissecting aneurysm of aorta. The probe extends from an opening in the media of the transverse portion of the arch into the false channel. A large thrombus occupies a sacular dilatation of the first portion of this channel. The channel then winds posteriorly around the aorta at the junction of the arch and thoracic segments and continues into the abdominal aorta (not shown). The false channel is partially endothelialized.
(Courtesy of Dr. Robert Fienberg, Beverly, Mass.)

the aortic valvular insufficiency which results from the proximity of the lesion to the aortic valve. Both of these variants will be discussed in the section dealing with pathogenesis.

Pathogenesis and Microscopic Pathology. Statistically, hypertension is present in the majority of cases of dissecting aneurysm (Burrell, 1955; Hirst *et al.*, 1956) and principally accounts for the left ventricular hypertrophy so frequently found at autopsy. Schnitker and Bayer (1944) found evidence of hypertension in 80 per cent of the 560 cases they reviewed, but of the 141 persons under the age of 40, only 50 per cent were hypertensive. Similarly, Gore and Seiwert (1952) found the incidence of elevated blood pressure significantly less in the younger age groups. Accordingly, the influence of blood pressure must be secondary (Mote and Carr,

1942), contrary to assertions (Logue, 1943) which unaccountably continue to appear (Halpert and Brown, 1955).

From the standpoint of transient elevation of pressure, neither trauma (Weiss, 1935), state of activity, nor exertion (Bauersfeld, 1947; McCloskey and Chui, 1951; Hirst *et al.*, 1956) have been shown to have a consistent relationship to the onset of dissection (Cherry and Cherry, 1941). Physical measurements of the bursting tension of the normal aorta indicate its ability to withstand pressures far in excess of even the most severe hypertension (Oppenheim, 1918; Klotz and Simpson, 1932; Moritz, 1932). Moreover, Robertson and Smith (1948) have found that the force required to produce artificial dissection exceeds 600 mm. of mercury. Intramural hemorrhage and dissection, therefore, can take place only in the presence of a seriously weakened vessel, a conclusion reached by Elliottson more

than 100 years ago (1830). Earlier students (Laennec, 1826; MacCallum, 1909) had regarded intimal disease as the basic weakening process. While it is true that atherosclerosis accompanying dissecting aneurysm is frequent and severe, especially among older persons, no consistent relationship exists between the site of the intimal laceration and the atherosclerotic plaques. Numerically, coincidence of a plaque and an intimal tear occurred in 2 of 85 cases (Gore and Seiwert, 1952) and in 6 of 218 reviewed by Shennan (1934). Furthermore, in young persons, there may be only an insignificant degree of intimal disease (Gore, 1953).

It is noteworthy that atherosclerosis is least severe in the proximal portion of the aorta, the very location in which dissecting aneurysms are most frequent.

On the other hand, structural changes do occur in the media which fully account for the weakening of the vessel wall in dissecting aneurysm. Occasionally, the prosector may observe that mere manipulation of the aorta produces cleavage of the media. Rottino (1939a) commented upon the linear intimal wrinkling which may occur over foci of medial degeneration just as it does in syphilitic aortitis. Recognition of medial involvement in dissecting aneurysm dates from Pen-nock (1839), Henderson (1843) and Rokitan-sky (1852). Histologically, degenerative changes in the media affect either the elastic or the muscle lamina, or both. Recognizing that the dissecting hemorrhage may have destroyed and exploited the areas of major structural weakness, it is still possible to find histologic evidence of preceding medial disease in virtually all cases. In each of 72 aortas examined microscopically a focal degenerative process was observed at multiple sites in the media (Gore and Seiwert, 1952). While such lesions were usually most severe in the region of the primary intimal tear in the arch of the aorta, they were also widely scattered throughout the length of the aorta and even in some of its branches.

Gsell (1928) was impressed by the regular occurrence of focal necrosis of muscle, traversed by the unaffected but condensed elastic laminae. Though he had also noted accumulations of inter-

cellular mucoid material, this feature was not predominant as it was in Erdheim's (1929, 1930) material. The latter described degenerative changes resulting in large gaps and defects in the elastic laminae, filled with mucoid material. Cellina (1931) related focal necrosis of muscle in the media to senescence, having demonstrated it in 9 of 10 aortas from persons over 72 years of age with minimal atherosclerosis.

Gore and Seiwert (1952) found that the degenerative process in the media in 72 cases could be divided into three groups: one primarily in-

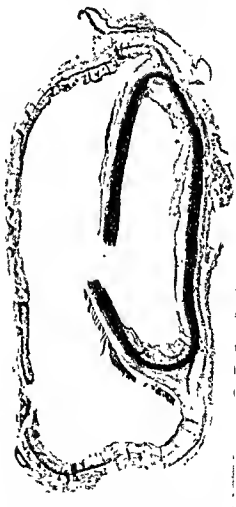


Figure XIV-23. Chronic dissecting aneurysm of aorta. Photomicrograph of a transection of the thoracic portion of the aorta shown in Figure XIV-21. The stained elastic tissue identifies the aorta which is partially enveloped by the false channel anteriorly (left portion of figure) and laterally. At the right, a split in the elastica indicates where cleavage had occurred. Note that intimal sclerosis involves the posterior wall of the aorta (right portion of aorta) and is virtually absent anteriorly.



Figure XIV-24 Acute dissecting aneurysm of aorta, without intimal tear.

volving the elastic laminae (16 cases), a second in which the muscular laminae bore the brunt of the damage (36 cases), and a third group of 20 cases in which both types of medial tissue were affected. Degeneration of elastic tissue proved to be predominant among the younger persons in the series, whereas the muscular defect was much more frequent among the older patients, as Cellina (1931) had established. Milder degrees of these structural changes are often observed in routine autopsy material (Rottino, 1939b, 1940), and is the basis for the belief that dissecting aneurysm is an exceptional complication of a fairly common process. The alterations appear to be slightly more frequent and severe in hypertension (Rottino, 1939b, 1940) and show a predilection for the ascending aorta and arch. Ashworth and Haynes (1948) described musculo-elastic medial degeneration in 23 of 40 persons with hypertension. However, their conclusion that the accompanying inflammatory and reactive features distinguish the hypertensive lesion from the process associated with dissecting aneurysm may be questioned. Ischemic degeneration may follow cleavage of the media and interruption of the vasa vasorum; such alterations are to be distinguished from the basic medial lesion underlying dissecting aneurysm.

Medial Degeneration Affecting the Elastic Tissue. This lesion is characterized by focal

loss of elastica, varying in extent from short segments of a few laminae to large "geographic" areas of the aortic media (Figure XIV-26). Frequently there is an associated increase of mucoid or chromatophilic material which in lesser amounts constitutes the normal ground substance (Bunting and Bunting, 1953; De Takats and Pirani, 1954). Erdheim (1930) was particularly impressed by its accumulation in cysts and cavities with evident compression of the adjacent lamellae. The tension of the aorta forces the semifluid mucoid material into the available structural defects and gaps in the media; accordingly, it is unnecessary to postulate primary overproduction of ground substance. Actually the quantitative variability or occasional absence of this material contrasts with the constancy of tissue degeneration and suggests that the latter is the initial morphologic change. As a consequence of the loss of elastic tissue, there is disalignment and retraction of the muscle fibers, an appearance which had been interpreted erroneously (Erdheim, 1930) as evidence of regeneration.

Medial Degeneration Affecting the Muscle. The type of degeneration which affects the muscle is more frequent, though micro-

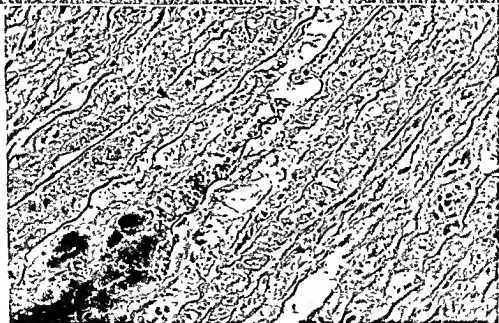


Figure XIV-25. Low-power view, showing medial degeneration of aortic wall. The midportion of the media is relatively pale and contains no nuclei. The muscular laminae have been lost, with resultant condensation of elastic laminae (unstained). (AFIP, photograph N-104314.)

Figure XIV-26. Medial degeneration of aorta. Focal disintegration and disruption of elastic lamina characterizes the elastic-tissue type of medial degeneration. (AFIP, photograph N-104291.)

Figure XIV-27. Medial degeneration of aorta. Note advancing wedge of intramural hemorrhage (lower left). Note accumulation of pale-staining intercellular material which distinguishes the cleavage plane. (AFIP, photograph N-104274.)

scopically less striking than the type that affects the elastica (Figure XIV-25). According to Gsell (1928), the muscle fibers of the aortic media normally insert into the elastic laminae and serve in an auxiliary fashion to prevent overstretching and to facilitate recoil of this tissue; as a result, changes in the arrangement of elastic laminae indicate degeneration of muscle. The elastic laminae lose their normally sinuous pattern; the fibers are more closely approximated because of the absence of intervening muscle and appear stretched and attenuated. The degenerative process is quite slow, leaving as inconstant vestiges of cellular disintegration, only tiny droplets of fat or a few granular deposits of calcium. Although the chromatropic or mucoid ground-substance may be increased, it does not accumulate in cysts as is often true with degeneration predominantly affecting the elastic tissue.

Where both forms of degeneration occur in the same aorta, individual foci may still show predominant loss of one or the other tissue.

Reactive Changes. With either form of medial damage, reactive tissue changes occur. Gsell (1928) noted that the "mucinous" material contained sparsely distributed stellate cells, and suggested that the material was reactive. The fibrous nature of the repair observed in older foci of medial degeneration supports his viewpoint. The reaction is entirely nonspecific, since various stimuli irritative to arteries produce an increase of "basophilic ground substance" (Core, 1952). The other components of the reparative response include vascularization of the media, relatively sparse perivascular infiltration of inflammatory cells, and adventitial fibrosis. These are features which are also common to syphilitic aortitis; but with syphilis, in addition to gummatous necrosis, inflammatory features are more marked, the vasa become virtually sealed by endarteritis, and fibrosis effectively knits the medial defect. It is noteworthy that syphilis does not predispose to dissecting aneurysms. By the same token, syphilitic infection does not prevent the co-

incidental occurrence of other forms of vascular disease.

The bland nature of the reparative reaction in idiopathic medial degeneration, revealed by contrasting it with syphilitic aortitis, is the key to the pathogenesis of dissecting aneurysm. The new-formed vasa are thin-walled, lie essentially unsupported in a weakened focus in the media, apparently vulnerable to rupture. The indirect pathway to the nutrient vessels delays the arrival of the pulse wave until that in the main channel has already passed. Were it not for this asynchrony, vasa vasorum arising from the adventitia could not function, let alone bleed, against the tension of the arterial wall. Numerous reports, dating from Schiede (1908), Moriani (1910) and Babes and Mironescu (1910), have indicated that intramedial hemorrhage (Figure XIV-27) does indeed occur from such vasa and can be the only tenable explanation for dissecting aneurysms without intimal tears. There is no histologic basis for segregating those with intimal lacerations, and these too must be regarded as originating intramurally. It seems likely that hypertension enhances the possibility of rupture of thin-walled, poorly supported vasa. Although hypertension is not essential for the development of dissecting aneurysm, its presence increases the possibility of medial degeneration and, in the later circumstance, augments the tendency to intramural hemorrhage (Rottino, 1939b; Ashworth and Haynes, 1948).

Clinically, dissecting aneurysm is a frequent mode of death in coarctation of the aorta (Abbott, 1928; Reifenstein *et al.*, 1947; Gross, 1953). Several examples of this anomaly, bicuspid aortic valve, and other congenital vascular defects, were noted in a series of 32 dissecting aneurysms in persons less than 40 years old (Core, 1953). Blackford (1928) made the pertinent observation that aortic rupture may occur even with slight degree of stenosis. The implication is that there is a congenital structural deficiency of the vessel wall which is more significant than the mechanical obstruction. Heath and associates (1958) believe that the hemodynamic stresses distal to a stenosed aortic valve (as described by Holman, 1954) contribute to medial degeneration, dilata-

tion, and dissecting aneurysms in the proximal aorta (McKusick *et al.*, 1957). Severe medial elastic tissue defects associated with aneurysmal dilatation have been described by Wolff (1932) in a 12-day-old infant and by Holle (1947) in a 3-month-old infant. Similar instances have been encountered in childhood and youth. Accordingly, delay in the onset of recognizable signs and symptoms does not rule out congenital influences. One can only speculate about the nature of a defect which may appear in the neonatal period or not until many years later. It is not possible to rule out a destructive process as the cause of gaps and breaks in the elastic and muscle laminae. However, the paucity of products of destruction and the predilection of the lesions for the proximal aorta suggest, alternatively, that they might arise from impairment of the metabolic mechanism responsible for the integrity of tissues subject to continuous stress. Although it has no apparent relation to human disease (Bean and Ponseti, 1955), there is an analogy in the production of lesions in the aortic arch of rapidly growing weanling rats fed with sweet pea meal (Bachhuber and Lalich, 1955) while no such lesion forms when this agent is fed to full grown rats that metabolically are less active. By contrast, the destructive effect of diphtheria toxin (Duff, 1932) was much more prompt and bore no evident relation to the age and rate of growth of the animal. Further investigation is warranted of Beaven and Murphy's (1956) observation that hypertensive patients treated with methonium had an unusually high incidence of dissecting aneurysms (8 among 44 patients).

Clinical reports suggest that there may be a relationship between pregnancy and dissecting aneurysm. In Schnitzer and Bayer's (1944) review, 24 of the 49 women under the age of 40 years were pregnant. However, Kinney and associates (1945) found that pregnancy did not increase the likelihood of aortic rupture in coarctation since this happened in only 3 of 39 reported cases.

Rare causes of dissecting aneurysm include mycotic infections (Lippincott, 1940; Bartol *et al.*, 1943; Williams, 1952) and granulomatous aortitis (McMillan, 1950; Brody and Krasnoff, 1956). Kountz and Hempelmann (1940) thought that myxedema was the cause of medial degeneration in 3 patients; however, lack of confirmation would indicate their findings to be coincidental

(Burchell, 1955). Gaylis and Laws (1956) warned that aortic dissection may complicate aortography when contrast media is injected into the vessel wall.

Mention has been made of the greater frequency of medial lesions in the proximal segment of the aorta as the basis for the disproportionate number of intimal tears that occur there. However, within that area there are two points of particular stress where intimal tears are most prone to occur: the ascending aorta as it crosses the right pulmonary artery, and the junction of the arch with the descending aorta (Shennan, 1934). In the first location, systole forces the aortic wall, which may be turgid and brittle from intramural hemorrhage, against the relatively unyielding right pulmonary artery. At the second site, the systolic impulse results in additional stress at the transition from a relatively mobile arch to the fixed descending aorta.

Traumatic Aneurysms

Traumatic lesions of the aorta result from sudden forceful compression of the thorax or from rapid linear deceleration such as may be experienced in falls from a height, or in motor vehicle or aeroplane crashes. Accordingly, it is in large part a "disease" of modern civilization. Among 7000 medicolegal autopsies, Strassman (1947) found 72 traumatic ruptures of the aorta. Eleven had multiple tears; of the 61 with solitary tears all but 3 were in the thoracic aorta and 38 were just distal to the insertion of the obliterated ductus arteriosus. A second vulnerable site was the first portion of the ascending aorta. Rice and Wittstruck (1951) have pointed out that in linear deceleration of the thorax, the central portion of the descending aorta, being the least rigidly bound, is snapped forward by the momentum of the body and the mass of the aorta's content of blood. Because there is more rapid deceleration of the proximal aorta which is fixed by the great vessels of the arch and the ligamentum arteriosum, great strain is exerted at its junction with the mobile descending segment. Similarly, the difference in fixation and mobility of the

heart and the first portion of the ascending aorta may account for the vulnerability of the latter site. The bursting pressure of the normal aorta exceeds 1000 mm. of mercury (Klotz and Simpson, 1932) and may be as great as 3000 mm. (Oppenheim, 1918). In the absence of structural weakness, then, the rupturing force must be great, to avoid its dissipation along the vascular channel, it must also be sudden.

Complete ruptures are, of course, promptly fatal but incomplete forms occur in which there is ample time for application of therapeutic measures. In autopsies of persons who have died as a result of severe trauma, it is not unusual to observe tears limited to the inner aspect of the aorta (Strassman, 1947, Stryker, 1948). Such lesions, occurring in nonfatal trauma, may heal by fibrosis and scarring and represent points of weakening, if sufficiently large and deep, stretching and herniation of the fibrous scar could result in formation of an aneurysm.

Indeed, Hollingsworth and associates (1952) reported 4 examples of saccular aneurysm of the aortic arch following severe chest trauma, all in young males who were followed for periods of a few months to 7 years. Steinberg (1957) observed 5 cases for periods ranging from 2 to 27 years. He noted that the sole fatality followed operative intervention for an aneurysm which had been asymptomatic for 5 years. In Stryker's (1948) case, an 18-year-old girl died 5 months following trauma with an infected aneurysm just above the aortic valve. Less frequently, as in the case reported by Leonard (1945), the aneurysm may be dissecting in type.

Clinical recognition of the condition requires a history of severe trauma involving the thorax, and radiologic evidence of widening of the superior mediastinum in the vicinity of the aortic arch. Holmes and Netterville (1956) stressed the significance of fractures of the first rib as evidence of chest trauma severe enough to cause serious injury to the mediastinal soft parts, including the aortic arch.

Arteriovenous Aneurysms

Arteriovenous Aneurysms, the result of ab-

normal communication between artery and vein, is a rare lesion predominantly affecting the vessels of the extremities, head or neck. Trauma is the most important etiologic factor, but at times infection or developmental anomaly may be responsible (Holman, 1937). The aneurysm is produced by enlargement of the arteries and veins proximal to the communication. Changes in pressure result in structural alterations aptly described as "venification" of artery and "arterialization" of vein (Holman, 1937). Of greater significance, however, but varying with the size of the fistula, are the changes compensating for the chronic "bleeding into the venous system," increased blood volume, and cardiac dilatation with hypertrophy. As a lesion involving the aorta, the condition is vanishingly rare. Three instances in the thorax, cited by Holman, are essentially late complications of aneurysms of the ascending aorta. Similarly his account of a mycotic aneurysm of the abdominal aorta suggests that its communication with the vena cava occurred late in its course.

Congenital Aneurysms

Lesions based upon faulty or anomalous development are described in Chapter VI, Sections C and II. Some of them deserve special emphasis, however, since they may not become manifest until well into adult life. With reference to the aorta specifically, aneurysms of the aortic sinus are often congenital; aneurysms related to coarctation are not infrequent; and arachnodactyly (Marfan's syndrome), a general disturbance of growth which includes hypoplasia of the aorta, is associated with an unusually high proportion of aneurysmal deformities.

Acquired aneurysms limited to the aortic sinuses are somewhat less frequent than the rare congenital ones. Of the 22 collected by Jones and Langley (1949), 17 were syphilitic, 4 were mycotic secondary to bacterial endocarditis, and one resulted from a dissecting aneurysm. Acquired lesions may arise from any of the sinuses and are usually larger than congenital lesions; they may arise cephal-

cally from the heart and tend to rupture extracardially (Merten *et al.*, 1956).

The "adult type" of *coarctation* of the aorta is particularly vulnerable to aortic rupture or dissection (Abbott, 1928; Shennan, 1934; Reifenstein *et al.*, 1947; Halonen and Aho, 1949, Gore, 1953; Gross, 1953). In 24 of the 104 cases reviewed by Reifenstein and associates (1947) the patient died as a result of the catastrophe. The tear lay proximal to the coarctation in 19 patients and distal in 5. Most commonly, the segment involved was dilated and unusually thin. Indeed a number of cases of aneurysm, some recognized during life, have been reported and illustrated with this anomaly as well as with the frequently associated bicuspid deformity of the aortic valve (Gore, 1953). The basic morphologic alteration is a depletion or destruction of the elastic lamina of the media, often accompanied by cystic accumulations of mucoid material. Hypertension, which is virtually always present proximal to the stenosis, is undoubtedly a contributory factor; but since ruptures and aneurysms (Moragues *et al.*, 1942; Zaslow and Krasnoff, 1943; Reifenstein *et al.*, 1947; Halonen and Aho, 1949; Cleland *et al.*, 1956) occur distal to the narrowing as well, hypertension cannot be regarded as essential. Other secondary factors contributing to the development of poststenotic aneurysms include medial damage from pressure of the "jet" intimal lesion (Edwards *et al.*, 1948) and the hydrodynamic principle that a "reduction of the velocity of flow through a cylindric channel is attended by an increase in the lateral pressure on the vessel wall distal to the constriction" (De Takats and Pirani, 1954; Holman, 1954). It has been noted that the poststenotic "jet intimal lesion" is a locus of predilection for bacterial aortitis, not a rare complication of coarctation (Reifenstein *et al.*, 1947; Edwards *et al.*, 1948). Indeed, one instance of a calcified poststenotic aneurysm has been regarded as a healed mycotic aneurysm (Reifenstein *et al.*, 1947).

Arachnodactyly, a rare familial and congenital disorder characterized by a tall slender habitus with disproportionately long

limbs and elongate thin digits, has been recognized as a clinical entity since it was described by Marfan in 1896 (Goyette and Palmer, 1953; Sloper and Storey, 1953; McKusick, 1955; Weiss *et al.*, 1956; Wilson, 1957). It affects both sexes equally; other physical features include a long thin face, dolichocephalic head, long pointed ears, protuberant jaw with long narrow teeth, a high arched palate, and hyperextensible joints. Ocular deformities, particularly dislocation of the lens and tremulous irides, occur in 50 to 75 per cent of individuals. As indicated in Table XIV-10, there are frequent cardiovascular lesions which often involve the aorta; less commonly other arteries may be affected (Austin and Schaefer, 1957). Valvular fibromyxomatous thickenings are often observed; and aortic insufficiency is common (Hirst and Bailey, 1956). Other congenital malformations are frequently found (Fischl and Ruthberg, 1951; Marvel and Genovese, 1951; Goyette and Palmer, 1953; Steinberg *et al.*, 1957), and include interatrial septal defects, coarctation, patent ductus arteriosus, and dilatation of aortic sinuses.

In most cases examined microscopically, the aorta presents medial degeneration, extensive loss of elastic lamina and accumulations of metachromatic material in cysts and clefts (Marvel and Genovese, 1951; Sloper and Storey, 1953). Medial vascularization and adventitial fibrosis are seen and presumably represent a form of repair. In any event, structural weakening accounts for the development of fusiform and dissecting aneurysms; most of these involve the ascending segment and arch of the aorta. Less commonly, the aorta may be hypoplastic with diminished circumference and structurally thin media (Whitfield *et al.*, 1951).

Mycotic Aneurysms

Mycotic Aneurysms of the aorta, the re-

TABLE XIV-10

Cardiovascular Lesions in 34 Cases of Arachnodactyly
(Goyette and Palmer, 1953)

Aortic Lesions	22	Valvular Lesions	27
Dissecting aneurysm	12	Mitral valve	15
Fusiform aneurysm	7	Aortic valve	10
Dilated aortic ring	3	Tricuspid valve	2

sult of bacterial (or fungal) infection of the vessel wall, are exceedingly rare. Parkhurst and Decker (1955) found a record of only 9 among 22,792 necropsies performed during the 50-year period, 1902 to 1951, at the Boston City Hospital. There were also 3 instances of bacterial aortitis, basically the identical process, uncomplicated by aneurysm. Their material also included 143 syphilitic, 92 atherosclerotic, 78 dissecting and 16 unclassified aneurysms.

All 12 cases of bacterial aortitis involved the thoracic aorta; 11 were in males, there was no particular age of predilection. The lesions varied in size from a tiny erosion or ulceration with rupture to a 10-cm. sac. Five of them were localized in the ascending aorta and represented extensions from bacterial infection of the aortic valve (Bartol *et al.*, 1943). In 2 others the aortic wall was infected from a contiguous structure (mediastinal abscess and mediastinal tuberculous lymphadenitis). These two groups correspond with Crane's (1937) secondary mycotic aneurysms. The 5 remaining cases were primary, defined as "a lesion developing in the wall of an artery which is not associated with any demonstrable intravascular inflammatory focus, as bacterial endocarditis, or with any inflammatory process in the surrounding tissues" (Crane, 1937). Four of the primary mycotic lesions were associated with remote infections (cellulitis of foot, pneumonia twice, and gonococcal arthritis), the source of the infection in the fifth case was not discovered. Some additional aortic diseases,

such as medial degeneration, atherosclerosis, syphilis, or congenital hypoplasia, invariably accompanied primary mycotic aortitis. In 2 cases, medial dissection extended from the site of the aortic infection similar to the instances reported by Lippincott (1940), Bartol and associates (1943) and Williams (1952). The route of bacterial infection of the aortic wall is obvious when the lesion is contiguous with vegetative endocarditis of the aortic valve or adjacent to an infected structure in the mediastinum. When the initial source is more remote, entry into the aortic wall by way of the nutrient vasa vasorum seems the likely explanation (Stengel and Wolferth, 1923; Rappaport, 1926; Owens and Bass, 1944). Entrapment of particulate infective fragments could be expected in smaller channels as they ramify and become narrowed, whereas surface implantation would seem to be hindered by the rapid flow of blood in the aorta. The presence of some other pathologic process seems to favor the occurrence of this rare complication; and in this regard it is pertinent to recall that increased vascularization of the aorta occurs in syphilis, atherosclerosis and medial degeneration. Microscopically, there is an exudative inflammatory reaction, often suppurative, leading to destruction of the media and weakening of the aortic wall. Rapidly progressive lesions perforate whereas in more indolent ones there is dilatation since time permits reinforcement of the weakened and dilated vessel by reparative fibrosis.

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Cardiopulmonary Disease

AVRILL A. LIEBOW

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THE VERY USE of the term "cardiopulmonary" implies a realization of the interdependence of the heart and lungs. An analysis of this relationship in its broadest sense will be attempted here. This concept is wider than the usual connotation of "cor pulmonale," but even the latter term has a vague boundary. Thus some observers, such as Courmand and Richards and their associates, use it to mean simply disease of the right side of the heart secondary to pulmonary disease (see Ferrer *et al.*, 1950) whereas others, such as Dexter and his group (1951), include the effects upon the right side of the heart of increased post-capillary resistance as occurs in mitral stenosis. Evidence is accumulating that an elevated post-capillary resistance may, in time, produce anatomic changes in the pulmonary vessels,

and perhaps even spasm. For this reason, the broader usage appears preferable.

Any attempt to unravel the complexities of cardiopulmonary disease* is made difficult by the fact that functional adjustments of significant mechanical degree may occur either late or early in the disease and yet leave few or no recognizable anatomic alterations. The upsets of both function and form must be studied if even a partial understanding is to be gained of cardiopulmonary disease in the living.

This presentation will include: (a) a general classification of cardiopulmonary disease; (b) a discussion of certain of the interrelated functional and anatomic aspects of pulmonary arterial hypertension; (c) a consideration of these factors as exemplified in certain diseases associated with cor pulmonale.

1. GENERAL CLASSIFICATION OF CARDIOPULMONARY DISEASE

While some conditions affect the heart and lungs simultaneously, far more often disease

of the lung is visited upon the heart, and disease of the heart, upon the lungs. If it be understood how disability of one of these organs affects the other, then the vicious cycles at work when both organs are simultaneously diseased become less difficult to comprehend (Table XV-1). The paragraphs that follow

* Out of need, the writer has sought the advice and criticism of friends and colleagues, who have given freely of their wisdom and time. He is especially indebted to Professor Alan C. Lendrum of Queen's College, Dundee, and to Dr. Allan V. N. Goodyer of Yale University. The errors and deficiencies that persist are the writer's own.

in this section are numbered or lettered to correspond to the listings in this table:

TABLE XV-1

Classification of Cardiopulmonary Disease

- I. Pulmonary disease affecting the heart, by
 - A Diminished pulmonary vascular cross-section
 - B. Inadequate oxygenation of blood
 - C Decreased mobility
 - D. Vascular shunts
 1. Bronchial arteries to pulmonary arteries
 2. Bronchial veins to pulmonary veins
 3. Pulmonary arteries to pulmonary veins
- II Cardiovascular disease affecting the lungs, by:
 - A. Increased resistance to pulmonary venous out-flow
 - B Congenital shunts
 1. Right to left (septal defects, drainage of systemic veins into left atrium)
 - 2 Left to right (septal defects, anomalous pulmonary venous drainage)
 - C Effects of other congenital anomalies
 1. "Systemic ventricle"
 - 2 Transposition of great vessels
 - 3 Conditions associated with diminished blood flow
- III. Conditions affecting the heart and lungs together.
 - A Infections
 - B. "Collagen diseases"
 - C Sarcoidosis
 - D. Overexpansion of blood volume
 - E Others

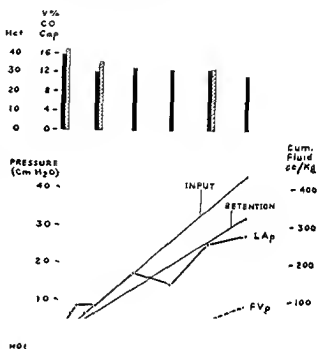
1. Pulmonary Disease as It May Affect the Heart

A. The factors that can increase the work of the right side of the heart include spasm, compression, narrowing, or physical loss of the vascular bed of the lung. Relatively slight diffuse changes are more likely to be detrimental than focal changes, for the reserve of the lung is large.

B. Inadequate oxygenation of blood in the lungs may result from the passage of blood through altered pulmonary substance (alveolar thickening, replacement by scar tissue, or filling by exudate or tumor), through poorly ventilated lung tissue (atelectasis, bronchial obstruction), or through a normal zone at too great a speed. This last takes place if the output of the right ventricle is made to pass at high pressure through too small a portion of normal lung (Adams *et al.*, 1953). Diffusion of gases in the lung as related to the circulation has been well discussed by Lilienthal and Riley (1954). The effects of the anoxia thus

induced are damaging to all organs, including the heart. Anoxia may also induce polycythemia and hypervolemia, with their attendant consequences: increased blood viscosity, increased tendency to thrombosis (with possibility of embolism), and increased cardiac output. Anoxia has been shown experimentally to result in cardiac enlargement (Barnard, 1958).

C. The function of the lung as an "accessory heart" and the abrogation of this function in pulmonary or pleural disease are discussed in Part 2 of this chapter.



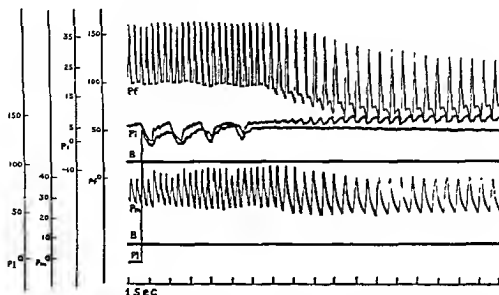


Figure XV-2. Effects of rapid distension of the peripheral end of the left pulmonary artery of a dog by the introduction of 100 ml of saline solution when the left pulmonary veins are occluded. Pressure in the left pulmonary artery (P_l) was raised from 0 to 142 mm. Hg. The systemic arterial pressure (P_f) dropped from a mean of 126 mm. Hg to 88 mm. Hg. The heart rate declined from 180 per minute to 90 per minute and the respirations were arrested, as seen in the tracing of intrapleural pressure (P_i). These changes had their onset simultaneously 6 seconds after starting the infusion. Pressure in the pulmonary trunk (P_m) fell 2-3 mm. Hg. This response to suddenly induced hypertension is reflex in nature since it is prevented by ipsilateral vagotomy. (From Downing, 1957.)

D. Various types of vascular shunts can develop in chronic pulmonary disease. Precapillary anastomoses may appear between the bronchial and pulmonary arteries with effects to be described in Part 2.

The bronchial veins can expand, especially in bullous emphysema, to a remarkable degree (Marchand *et al.*, 1950; Liebow, 1953). Normally, these veins form a bridge between the pulmonary and azygos venous systems, carrying blood from the left to the right side (Zuckermandl, 1881). When, as in emphysema, however, there is right-sided cardiac failure with increased systemic venous pressure, and the valves become incompetent as the vessels increase in diameter by a factor of 2 or more, it is possible for these bridging vessels to constitute an extrapulmonary right-to-left shunt that may contribute to desaturation and hypercapnia of the systemic arterial blood. The volume of such a possible shunt has not as yet been accurately measured.

Precapillary shunts between small pulmonary arteries and veins are said to exist in the normal lung (Tobin and Zariquiey, 1950; Rahn *et al.*, 1952), but functionally important

congenital arteriovenous shunts are rare (Yater *et al.*, 1949; Lindskog *et al.*, 1950; Gray *et al.*, 1952). Unless present in military form (Hales, 1956), they do not constitute a direct burden to the right heart. Complications typical of the polycythemia that is associated with the decreased oxygen tension may, however, appear.

It is apparent that the main effect of the various malfunctions induced by pulmonary disease is to increase the work of the right side of the heart. Left ventricular hypertrophy has also been observed under such circumstances in the absence of systemic hypertension (Parker, 1940; Scott and Garvin, 1911; Spain and Handler, 1946; Spatt and Grayzel, 1948). There is good evidence that hypertrophy of the walls of the chambers occurs independently. The explanation of the left-sided cardiac hypertrophy has, therefore, been sought in the increased cardiac output that may be observed in chronic pulmonary disease. Another contributing, or determining, factor may be the development of a collateral circulation which, as it pursues the circle, left side of the heart—aorta—bronchial arteries—

pulmonary capillaries—pulmonary veins—left heart, constitutes a burden upon the left ventricle alone (Figure XV-45).

II. Cardiovascular Disease Affecting the Lungs

A. An increase in resistance to outflow from the pulmonary capillaries may result from cardiac disease, such as mitral stenosis, or from left heart failure in general. Obstruction to pulmonary veins is rarely important as such, unless diffuse and subtotal (Edwards and Burchell, 1951). This may be acquired, as in compression by tumor, or it may be of congenital origin. Complete venous obstruction in a lobe or lung produces an abundant collateral circulation (Hanlon *et al.*, 1952; Wyatt *et al.*, 1953; Hurwitz *et al.*, 1954a, b). Simple increase in pulmonary venous pressure seems not to be so efficient in this respect.

Rapid restriction of pulmonary venous outflow will lead to pulmonary edema near the point where the capillary pressure becomes raised to that of oncotic pressure. This may happen, for example, in severe bradycardia (G. S. Campbell *et al.*, 1949; Harrison and Liebow, 1952). The pulmonary edema occur-

ring when the left ventricle is failing, is often reversible, but may terminate fatally. In slowly developing chronic obstruction, as in mitral stenosis, much higher intracapillary pressures can be tolerated without accumulation of fluid in the alveoli, but the lung is damaged in other ways (see Part 3 of this chapter). Mechanical factors are frequently superimposed upon others that contribute to the development of edema. Pulmonary edema leads to anoxia and its consequences. Pulmonary arterial hypertension and associated phenomena accompany the rise in pulmonary venous pressure.

B. Septal defects in the heart may exert an influence upon the lungs, depending on direction of the shunt. Right-to-left shunts lead to decreased systemic oxygen tension, polycythemia, and other consequences. When the shunt is predominantly from left to right, pulmonary blood flow is increased, with consequences to be discussed. The effects of anomalous venous drainage from the lungs into the right atrium or its tributaries are similar. Whether increased flow as such, without increased pressure, can damage vessels is still under consideration.

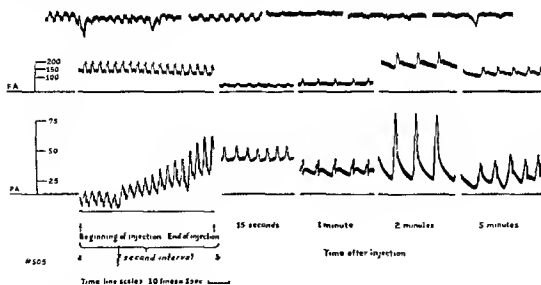


Figure XV-3. Effects of fat embolism in the dog. Segments of pressure recording (retouched for photographic contrast) showing the effects of the injection of 1.5 ml. of fat per Kg. of body weight. The uppermost tracing is of intrapleural pressure, small deflections were produced by cardiac action, large ones by respiration. The middle tracing is of femoral arterial (FA) pressure. The lowest represents the pressure in the pulmonary trunk (PA). Early rise of PA pressure is shown during injection, with a slight downward trend in the FA. There were apnea, bradycardia, systemic hypotension and persistent pulmonary hypertension at 15 seconds. Gradual re-establishment of PA and FA pressures occurred over the next 5 minutes and respirations returned. (From Halasz and Marasco, 1957.)



Figure XV-4 (left). Extreme dilatation of pulmonary arterial trunk proximal to stenosis produced experimentally in a puppy within 48 hours of birth, 20 weeks previously. The pressure in the trunk was 180/85 mm. Hg (117 mm. Hg mean). (From Liebow *et al.*, 1950a.)

Figure XV-5 (right). Same animal as in Figure XV-4 at post-mortem. The diameter of the pulmonary arterial trunk is 3 times as great and its wall is thicker than that of the aorta at the same level.

C. Pulmonary hypertension will also occur when the pulmonary trunk is subjected to the same pressure as the systemic aorta—as in truncus arteriosus or in common ventricle; when the pulmonary trunk is made to carry blood to the systemic arteries, as in aortic atresia, and in some types of coarctation of the aorta, and in instances of transposition of the great vessels (J. A. Campbell *et al.*, 1949) where pulmonary arterial pressure actually exceeds the systemic arterial pressure.

When the pressure in the pulmonary arteries is diminished, bronchial collateral circulation is stimulated. Low pressure, especially when there is also polycythemia as in tetralogy of Fallot, is often associated with thrombosis of pulmonary arterioles (Hales and Liebow, 1948; Rich, 1948).

III. Conditions Affecting Heart and Lungs Together

Relatively little further discussion need be given to conditions that affect the heart and lungs together, since the principles governing the influence of one organ upon the other are no different than those considered in the two preceding sections.

A. Infective agents producing pneumonitis, such as the rickettsiac, may also produce myocarditis; with others, a direct action upon the myocardium is less obvious, although it may exist. The heart can also be indirectly affected by the pulmonary disease as a consequence of the attendant anoxia, by the fact that the diseased lung is impaired as a blood pump, and by other factors.

B. The myocardium and lung may be involved together in certain of the "collagen diseases" and the damage may be especially striking in scleroderma.

In *polyarteritis*, small pulmonary arteries may be involved as part of the general vascular disease. It sometimes happens also that the respiratory tract, as in Wegener's granulomatosis, or in the "angitis and granulomatosis" described by Fienberg (1953) may be predominantly, or even exclusively, involved. The problem of the identity or separateness of these conditions has not as yet been resolved.

In *lupus erythematosus*, the recurrent "fitting pneumonitis" may be not dissimilar to ordinary bacterial pneumonia, but vascular and collagen changes have also been described.

Acute rheumatic carditis is rarely, if ever, ac-



Figure XV-6 (left). Trunk of pulmonary artery proximal to the constriction in animal shown in Figures XV-4 and 5. The wall here is more than 5 times as thick as in the distal segment (Figure XV-7). In the region of hypertension, elastic lamellae are more numerous than distally, but there is focal medionecrosis. X 30.

Figure XV-7 (upper). Segment of pulmonary artery distal to point of constriction, where the pressure was normal or below normal. Here the elastic lamellae are thin and regular. Muscle is less abundant than proximally. X 30.

accompanied by pneumonitis ascribable on histologic grounds to "allergy." Changes in the lungs are largely the result of passive congestion (see Part 3 of this chapter).

In *rheumatoid arthritis*, typical "nodules" may involve the heart and pleura (Ellman *et al.*, 1954) and lung (Christie, 1954). It has been suggested that fibrosing focal pneumonitis may indicate rheumatoid damage (Price and Skelton, 1956, Edge and Richards, 1957), but the relationship is uncertain.

C. The lesions of sarcoid can displace or replace much of the myocardium, as well as the lung, and scarring may ultimately involve both organs. In the lung, this may lead to obliteration or compression of the pulmonary vessels. In addition, the walls of the distal air passages may become thickened and distorted.

This results in air trapping and emphysema or, when the process is in the most distal distribution, in the syndrome of "alveolo-capillary block."

D. Intravenous injection of excessive fluid, particularly blood, may produce overexpansion of blood volume which is important clinically. In extreme instances, the venous pressure will rise and it is of interest that the pulmonary venous pressure rises much more steeply than the systemic venous pressure (Figure XV-1). Elevated venous pressure affects both the heart and lungs. Overexpansion of blood volume alone rarely causes pulmonary edema but, acting in concert with other accompanying factors, such as hemodilution, often quickly produces massive edema of the lung.

2. INTERRELATIONSHIPS OF PULMONARY AND CARDIAC FACTORS IN PULMONARY HYPERTENSION

The pressure in the pulmonary arteries is determined by the resistance to right ventricular output as related to volume of flow, and

to the viscosity of the blood (see Burton, 1952). Under normal circumstances, the systolic pressure does not exceed 25 mm. Hg, the



Figure XV-8. Angiogram at time of admission of 10-year-old boy with common "ventricle," demonstrating an enormous aneurysm of the pulmonary arterial trunk which arises to the right of the aorta in a "transposed" position.



Figure XV-9. Thick-walled sac of aneurysm of the trunk of the pulmonary artery seen in Figure XV-8. Dissecting hemorrhage is visible through the outer coats. The pulmonary artery is thicker and from 3 to 4 times the diameter of the aorta which is anterior in position and displaced sinistrally. The superior vena cava is displaced to the right.

diastolic 8 mm. Hg, nor the mean 15 mm. Hg (Courmand, 1950-51). In contrast to the systemic capillaries with their hydrostatic pressure not far off the oncotic, the pulmonary capillaries have a low hydrostatic pressure which must surely reduce the likelihood of pulmonary edema.

It has been established by direct microscopic examination that only a portion of this bed is perfused at any one time under basal circumstances (Hall, 1925; Wearn *et al.*, 1934). Expansibility of the normal pulmonary vascular tree, by opening up of additional channels or by dilatation of those already operative, is enormous, so that as much as a three- or four-fold increase in blood flow over the normal of 3.1 liters per square meter of body surface can be accommodated without a rise in the pulmonary arterial pressure (Hickam and Cargill, 1948; Riley *et al.*, 1948; Courmand *et al.*, 1950). This expansibility is also seen in functional studies (Courmand *et al.*, 1950) after resection of a diseased lung. The remaining lung, presumably free of disease, becomes larger, especially in deep expiration, and the maximum breathing capacity is found to be reduced, but only to 63 per cent. Total pulmonary blood flow and pulmonary arterial pressure are normal at

rest. In certain patients, the remaining lung may be normal, in all respects, to the various tests.

The structure of the normal pulmonary arteries reflects the low pressure within them. This is a specific instance of the more general biologic fact that vascular architecture is modified by flow and pressure (Thoma, 1911). If the relatively high pressure of fetal existence is maintained because of some structural anomaly or if pulmonary hypertension develops from any cause, the walls of the vessels become modified, sometimes in a manner that may actually contribute further to pulmonary hypertension, as will be detailed.

In the genesis of pulmonary hypertension, the synergistic interaction of pulmonary and cardiac abnormalities is well exemplified. While any one may not be sufficient in itself to burden the right side of the heart, the sum

of their effects may well lead to pulmonary hypertension and cardiac failure.

The nervous system apparently is involved in bringing about this detrimental synergism. Thus the series of reflex phenomena that follow rapidly produced distension of the vessels of one lung are abolished by homolateral vagotomy, these reflex changes include bradycardia, a fall in systemic arterial pressure and apnea, or rapid shallow breathing (Churchill and Cope, 1929, Downing, 1957) (Figure XV-2). Such observations support the suggestion of a neurogenic component in the pathogenesis of the "acute cor pulmonale" that follows sudden occlusion of pulmonary vessels. Thus, in experimental fat embolism, a precipitous rise in pulmonary arterial pressure is accompanied by a fall in systemic pressure and by apnea (Figure XV-3), but the changes in pulse rate are more variable (Halasz and Marasco, 1957). It is uncertain whether the fall in systemic pressure is the result of a reflex or the consequence of diminished cardiac output. Various, often concomitant, factors in pulmonary hypertension may be listed (Table XV-2) and these will be discussed in turn:

TABLE XV-2

Factors in Pulmonary Hypertension

- I Diminished total pulmonary vascular cross-section
 - A. Spasm
 - B. Vaso-restrictive changes
 1. Intimal proliferation
 2. Changes in elastica
 3. Muscular hypertrophy and hyperplasia
 4. Arteriolitis
 5. Fibrinoid changes
 6. Thrombosis
 - C. Embolism
 - D. Compression
 - E. "Loss" of vessels
- II. Increased postcapillary resistance
- III. Development of shunts: bronchial arteries to pulmonary arteries
- IV. Decreased efficiency of respiratory blood pump
- V. Increased blood viscosity
- VI. Increased flow

I. Diminished Pulmonary Vascular Cross-section

The anatomic evaluation of the total vascular cross-section presented to the output of the right ventricle is a matter of the greatest

difficulty and has not been adequately achieved. At present, a better estimate of its relative size can be obtained by functional measurements. This cross-section can be reduced reversibly by spasm, or permanently by anatomic changes.

A. SPASM

1. Effects of Anoxia. Evidence has accumulated that a decrease in the oxygen tension in the inspired air or an increase in alveolar $p\text{CO}_2$ can produce spasm of the pulmonary vessels. Such an effect has been demonstrated in the intact cat by von Euler and Liljestrand (1946) and in isolated lungs by Nisell (1950)



Figure XV-10 (upper). Recent and old dissections of the trunk of the pulmonary artery. Just proximal to the origin of the left pulmonary artery (which is at the right margin of the photograph above the metric scale), is seen the elevated lip of a completely healed dissection. The floor of the dissection is smooth and fibrous (compare with Figure XV-11). More proximally, near the lower margin of the photograph at the left, is a more recent dissection infiltrated with blood.

Figure XV-11 (lower). The dissection is seen microscopically to have occurred within the outer strata of the media. The elevated lip of the dissection corresponds to Figure XV-10. The floor is buttressed by a thick layer of fibrous connective tissue.



Figure XV-12. Wall of pulmonary artery at a distance from the dissection, showing medionecrosis. The similarity to Figure XV-6 from the experimental animal is striking. In the human instance, the pressure 4 years before death was 90/47.

and by Duke and Killick (1952). Furthermore, by the use of the bronchspirometric cannula and analysis of blood gases, a shift of blood to a lung respiring gases with normal or high oxygen tension from a hypoxic lung has been demonstrated (Dirken and Heemstra, 1948; Peters and Roos, 1952). In man, however, Fishman and his collaborators (1955), using similar methods, did not find a shift of blood from a lung respiring 10 per cent oxygen in nitrogen to the side respiring gases slightly higher in oxygen concentration than air. In the hypoxic intact animal, the demonstration of increase in the pulmonary arterial-venous pressure gradient without significant rise in blood flow would be necessary in order to prove that a rise in the pulmonary arterial pressure was the result of vascular spasm, rather than left heart failure. This has in fact been accomplished in the dog by Lewis and Gorlin (1952) and by Stroud and Rahn (1953), and in man by McGuire and associates (1951). But if the hypoxia is extreme,

e.g., sufficient to reduce the systemic arterial oxygen saturation of the dog to below 53 per cent, then, as Lewis and Gorlin have shown, the peripheral resistance in the lung is actually decreased while the cardiac output increases.

Evidence for the existence of a vasospastic factor related to hypoxia in certain types of pulmonary disease in man, especially emphysema, is discussed in Part 3 of this chapter. Of particular interest is the occurrence of "mountain sickness" with *cor pulmonale* in the natives of the high Andes (Rotta, 1947; Hurtado, 1955).

It appears that high peripheral resistance in the pulmonary vessels depends not upon a desaturated state of the systemic arterial blood, but rather a fall in the alveolar pO_2 . As demonstrated by Nisell (1951), perfusion of the isolated lung with hypoxic (or hypercapnic) blood actually reduces the pulmonary vascular resistance.

2. Evidence for Spasm in Pulmonary Arterial Hypertension. It was well known to the older pathologists that hypertrophy of the right ventricle was often observed in longstanding fibrosing pulmonary disease. The existence of pulmonary arterial hypertension not associated with obvious disease of the pulmonary parenchyma has only gradually come to be realized.

Monckeberg (1907) was the first to establish histologically an instance of hypertension associated with pulmonary vascular rather than parenchymal disease. Several massive reviews have appeared at intervals (Posselt, 1909; Ljungdahl, 1915; Brenner, 1935) in which the subject is discussed at some length. Steinberg (1929) was among the earliest to state that the vascular lesions might initially be the result, rather than the cause, of the high pulmonary arterial pressure, just as had previously been suggested as the probable sequence in systemic hypertension.

The term *primary pulmonary hypertension*, or *primary pulmonary arterio- or arteriolar sclerosis*, has come to be applied to cases in which the changes cannot be attributed to previous parenchymal disease.

Direct evidence for the existence of a vasospastic element in primary pulmonary hypertension and, with it, the implication of par-

ticipation of the autonomic nervous system was not forthcoming, however, until it was demonstrated that such substances as tetraethylammonium, priscoine (tolazoline hydrochloride) and acetylcholine could, in some patients, temporarily diminish pulmonary vascular resistance with resulting increase in the cardiac output from initially low values (Fowler *et al.*, 1950; Dresdale *et al.*, 1951, 1954; Harris, 1957; Wood *et al.*, 1957). This is of special interest since the difficulty of exploration of the function of the abundant pulmonary nerves has been of Himalayan proportions.

Evidence for the existence of pulmonary vascular spasm, presumably neurogenic, has been obtained by the methonium method, even in the hypertension associated with mitral stenosis (Goodwin, 1956). Acetylcholine recently has also received attention as an agent competent to reduce pulmonary arterial pressure under certain conditions (Harris, 1957; Wood *et al.*, 1957). The mechanisms concerned require further investigation.

B. VASORESTRICTIVE CHANGES

On the basis of the evidence just cited and because the anatomically demonstrable lesions may be minimal (DeNavasquez *et al.*, 1940; East, 1940), it appears probable that at least some instances of "primary hypertension" begin with vascular spasm. In other instances, various lesions classified here as vasorestrictive have been described.

Although it is possible that such lesions might develop spontaneously on the basis of an unknown pathogenesis and thence advance to the point of significant restriction of the pulmonary vascular bed, it is now well established that any of them may be secondary to hypertension induced by excessive flows as in Eisenmenger's complex (Eisenmenger, 1897; Cavin and Edwards, 1950; Old and Russell, 1950), patent ductus arteriosus (Welch and Kinney, 1948; Wood, 1952; Cosh, 1953; Heath and Whitaker, 1955), coarctation (Edwards *et al.*, 1949), common ventricle, or septal defect (Braunstein, 1955), or by an increased post-capillary resistance, as in mitral stenosis (Brumm, 1901; Parker and Weiss, 1936; Lendrum, 1956), or by pul-

monary venous obstruction (Edwards and Churchill, 1951).

In various forms of congenital heart disease with a left-to-right shunt, the increasing resistance induced in the pulmonary vessels by the restrictive changes within them will sometimes induce a late reversal in the direction of the shunt, whereupon the prognosis becomes ominous. Such vascular lesions may also be superimposed on embolic phenomena after a sufficient restriction of the pulmonary vascular bed has taken place.

Pulmonary arterioles also can become altered under the influence of an experimentally induced hypertension (Muller *et al.*, 1953; Ferguson and Varco, 1955).

It may be concluded that the presence of anatomically striking vasorestrictive lesions in "primary hypertension" does not negate the possibility that here, also, they may be secondary to the excessive pressure,—in this instance probably induced by spasm of the vessels.

The factors that initiate the spasm are, at this time, totally unknown. The disease may appear at a very early age (Figures XV-21, 38, and 39; Adams, 1952; Berthrong and Cochran, 1955), and it has even been questioned whether right-sided cardiac hypertrophy in the newborn might not be explained by primary pulmonary hypertension in some in-



Figure XV-13. Atheromatous changes in a major pulmonary artery in pulmonary hypertension initiated by embolism from thrombophlebitis of the left arm in a 40-year-old woman.

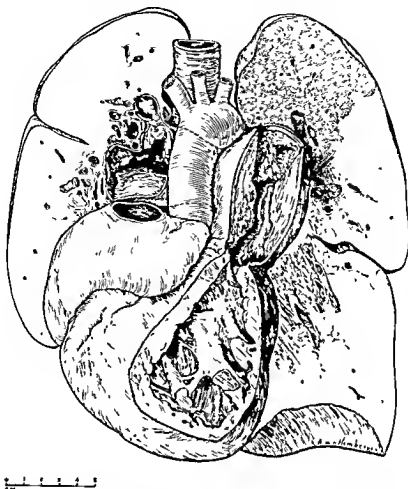


Figure XV-14. Heart and lungs in presumably "primary" hypertension of at least 6½ years' duration. The patient was a woman, aged 33 years at death. The pulmonary trunk exhibits striking atheromatous changes. It is enlarged, thick-walled, and partly filled with laminated clot. Clot is visible also in its branches within the right lung. This mural thrombus may act as a source of emboli to peripheral pulmonary vessels. Some vessels of small size contain thrombi in various stages of organization; others show marked muscular hypertrophy and hyperplasia.

stances (Wolman, 1950). The pathogenesis of the process in embryonic life is especially difficult to understand, under circumstances when the lungs are, to some extent, bypassed by the patent ductus and foramen ovale (Barclay *et al.*, 1944; Barcroft, 1947).

Although the various arterial lesions will be discussed principally as seen in "primary hypertension," reference will frequently be made to their occurrence in various forms of secondary hypertension. Most of the features of these lesions were well described by Staemmler (1938) on the basis of his own observations (1937) and on those of Bredt (1932), Hoenig (1937), Wiese (1935-36), Steinberg (1929) and others. Staemmler answered in the affirmative the question posed in the title of his 1938 article, "Does

primary hypertension exist in the lesser circulation?" and indicated that the stages following persistent spasm of the arterioles were, in order: hypertrophy of muscle, damage to elastic fibers, necrosis of muscle, and formation of thrombi. "Organically fixed hypertension" was thought to be the end stage of this process. These changes were held to contribute in varying degree to an increase in the thickness of the wall, and to restriction or obliteration of the lumen. Schmidt (1953) reviewed earlier concepts, and suggested that obstructing lesions can develop in veins as well as arteries and that this might account for hemosiderosis of the lung in some of these patients.

While normally arterioles or, better, precapillaries of the lung of an external diameter

of less than 100 micra are remarkably thin-walled structures consisting only of endothelium supported by a thin elastic lamina (Brenner, 1935; Civin and Edwards, 1951), in hypertension such vessels may resemble the altered peripheral arterioles of comparable size in systemic hypertension (Figure XV-19). It is necessary to distinguish such altered pulmonary vessels from bronchial arteries with which they have frequently been confused. The position of the bronchial arteries in the lamina propria of the larger bronchi and the predominance of longitudinal muscle in their inner walls should serve as a clue to the difference (Weibel, 1958). This longitudinal muscle becomes remarkably proliferated when these vessels enlarge (Liebow *et al.*, 1953). In the periphery of the lung, the two arterial systems, especially when altered by disease, may be difficult to distinguish unless traced to their sources. This is best accomplished by injection methods.

Experimental studies have provided evidence that pulmonary vessels can reflect in their structure the pressures to which they were subjected during life. Thus, if, in newborn puppies, stenosis of the pulmonary artery is produced severe enough to raise the pressure in the pulmonary trunk to levels approximating or exceeding those in the aorta, the vessel becomes thicker and increases in size, in striking contrast to the segment

distal to the obstruction where the pressure is, if anything, lower than normal and which comes into a state of "post-stenotic dilatation" (Figures XV-4 to 7) (Liebow, Harrison and Hales, 1950). In the thickened segment, the elastic lamellae are more numerous, but often appear frayed or show defects ("medionecrosis") and focal replacement by fibrous connective tissue which can become chondrified or calcified. Muscle is more abundant in the proximal segment. Distal to the stenosis, the elastic lamellae are thin and regular.

Most of these changes are analogous to those which may occur in extreme pulmonary arterial hypertension in man, as in common ventricle (Figures XV-8 and 9). As in the aorta, a dissecting aneurysm may form in association with medionecrosis of the pulmonary trunk (Figures XV-10 to 12). The fact that these changes occur in the pulmonary artery at levels of pressure that would be normal in the aorta poses an unsolved biologic problem of great interest. Loss of elastica associated with Marfan's syndrome can lead to aneurysmal dilatation of the pulmonary artery (Tung and Liebow, 1952).

Having considered one experimental analogue, the various vascular changes in pulmonary hypertension will be individually considered, with the understanding that several or all may be seen at once. Although it is probable that hypertrophy of the muscularis

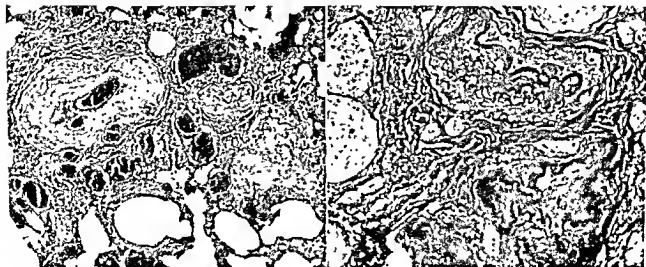


Figure XV-15 (left). Marked fibroelastic "hyaline" changes of the intima with restriction or obliteration of the lumen. The apparent recanalization in the largest vessel may be the result of organization of blood clot. The smaller arteries (arrows) appear collapsed. (Compare with Figure XV-16.) X 50.

Figure XV-16 (right). Verhoeff's elastic stain of the smaller vessels shown in Figure XV-15. Note thickening and reduplication of elastic laminae and the obliterated lumen. X 115.



Figure XV-17 (*left*). Concentric increase in subendothelial connective tissue with reduction of lumen. The symmetry of this change suggests proliferation of fibroelastic tissue, rather than organization of thrombus, as the responsible mechanism. X 140.

Figure XV-18 (*right*). Further section in an uninterrupted series of the vessel shown in the preceding figure, with total interruption of the lumen at this level, the result of gradual apposition of the walls. Such a process may be associated with obliteration of more distal branches. X 140.

is the initial anatomic sign of pulmonary hypertension, the changes in the various coats will be considered systematically, beginning with the intima.

Intimal Proliferation and Atherosclerosis. Atherosclerosis occurs especially in the larger arteries (Figure XV-13) and is occasionally seen in small arterioles. The incidence and extent of the atherosclerosis of the major pulmonary arteries increases with advancing years and is almost universally present in minor form after the age of 40. Its extent is independent of coronary or aortic sclerosis. There is no doubt, however, that pulmonary hypertension accentuates the process. Although such atherosclerotic changes early drew attention to the association of pulmonary arteriosclerosis and right cardiac failure that has often been referred to as Ayerza's disease, they are not functionally significant in themselves. The lesions in the largest arteries may become ulcerated and the seat of mural thrombi that may then seed the branches with further restriction of the vascular bed (Figure XV-14).

Endothelial proliferation and accumulations of connective tissue are often seen in company

with other changes (Brill and Krygier, 1941). From the observations of Harrison (1948, 1951), Barnard (1954), Thomas and O'Neal (1956a, b), and their respective co-workers, it may be asked whether such "endarteritis" may not, in part or in whole, result from organization of thrombi (Figure XV-15). In some vessels the reduction of the lumen by a symmetrical increase in connective tissue suggests another and perhaps reparative process (Figures XV-17 and 18). Changes of this type may also occur in consequence of obliteration of the peripheral vascular bed, or of a proximal block. It is impossible to establish the mechanism without serial sectioning.

Elastica. Elastic tissue may form abundantly in remnants of organized emboli that ultimately come to have the appearance of intimal plaques. Other processes less well understood may, likewise, contribute to the increase of this tissue, often in concentric or interlacing laminae among sheets or groups of muscle fibers in the media (Figure XV-16). In other instances, elastica may disappear focally or completely. Medionecrosis associated with pulmonary arterial hypertension has already been discussed.

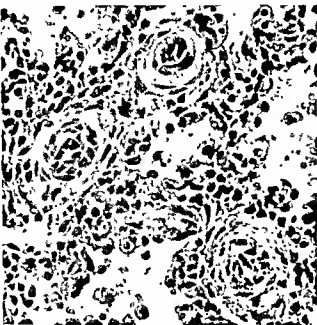


Figure XV-19. Pulmonary arterioles in an instance of coarctation of the aorta proximal to a widely patent ductus in a child 2 months of age. The muscle cells of the media are large and clearly in several layers. The diameter of these vessels to the external margin of the media varies from 31 to 47 micra. Normally, vessels of this size have few or no discernible muscle cells in their walls and consist essentially of endothelial cells supported by an elastic lamina X 290.

Muscular Hypertrophy and Hyperplasia. The hypertrophic and hyperplastic state of the muscle seen most prominently in the media, when generalized, probably represents the anatomic expression of the increased tonus that obtains in hypertension (Figures XV-19 to 21). It is remarkable that such changes may develop in the first few months of life, and to an extent greatly in excess of the normal muscular state of the pulmonary vessels at birth, and that they may be associated with massive right ventricular hypertrophy in such instances.

Although the presence of a thick intimal layer of longitudinally arranged muscle occurs characteristically in expanded bronchial arteries, this may be seen also in pulmonary arteries, especially when in free anastomosis with the bronchial arteries. Such changes may occur focally, as is true of medial hypertrophy in the absence of hypertension.

Fibrinoid Changes. Deposition of "fibrinoid" in any of the layers of the vessel may take place in extreme pulmonary hypertension, i.e., at levels approaching pressure in the sys-

temic arteries. When it occurs, there is also often necrosis (Figures XV-22 to 24). The mechanisms concerned in the formation of fibrinoid are not clear, except that there are indications that the material is derived from the blood (Brunson *et al.*, 1955). In the systemic circulation, extreme spasm with hypertension associated with administration of norepinephrine may produce fibrinoid changes in systemic arterioles with great rapidity (Waters and de Suto-Nagy, 1950). Fibrinoid changes in pulmonary arteries are sometimes seen also in the various forms of allergic vasculitis in such conditions as Wegener's granulomatosis and lupus erythematosus and, according to Lendrum (1958), are common in infarcts. Good fixation in formol-sublimate and special stains such as the picro-Mallory are sometimes necessary to demonstrate these changes.

Necrosis of "Arterioles" and "Arteriolitis." In some instances of extreme pulmonary hypertension, the arterioles become largely necrotic and heavily infiltrated with polymorphonuclear leukocytes, as well as mononuclear



Figure XV-20. From the same lung as shown in Figure XV-19. Larger arterioles showing a thick muscular medial coat, and a strikingly thickened adventitia, even for this age. X 50.



Figure XV-21. Pulmonary arteriole from a 5-week-old child with primary pulmonary hypertension. Greatly thickened muscular media. Serial sections showed no evidence of occlusion of the peripheral branches of these arterioles. Smaller arterioles possess less elastica. Verhoeff's elastic stain. (See also Figures XV-38 and 39) X 145.

cells (Figures XV-25 and 26). The resemblance to the lesions of periarteritis nodosa or "sensitivity angitis" is striking. Evidence against an allergic pathogenesis is that such altered vessels occur not only in primary hypertension, but also in Eisenmenger's complex (Old and Russell, 1950), patent foramen ovale (Braunstein, 1955), and in chronic long-standing mitral stenosis (Lendrum, 1956). The fact that such diverse conditions produce the same effect suggests that high pressure is the pathogenetic mechanism.

Necrosis of the wall may be associated with fibrinoid changes described, and with thrombosis, in various stages of organization (Figure XV-27). As healing progresses, portions of the former muscular wall may be replaced by hyperplastic connective tissue (Figure XV-28), or may even become aneurysmally expanded. Such changes have been regarded as "congenital defects" by some (Gilmour and Evans, 1946; Spencer, 1950), and have served as the basis of a theory that the pathogenesis of the "primary hypertension" is thrombosis or connective tissue hyperplasia over such "weak spots," with ultimate restriction of the lumen.

The best evidence that this is not the case but rather that the defects are the result of necrosis is, again, the fact that they commonly occur in secondary hypertension (Figures XV-27 and 28).

Barnard (1954) has also produced such changes experimentally by injection of blood clot with the consequent development of hypertension, which may have as secondary effects the necrotizing and other lesions that have been described.

Thromboangiitis, "Plexiform" and "Angiomatoid" Lesions. Thrombi are often found in arterioles in pulmonary hypertension and may or may not overlie other mural lesions (Figure XV-27). They may even be seen in the pulmonary trunk in association with atheromatous transformation of the intima, whence emboli may be derived (Figure XV-14).

Among the most remarkable changes are the plexiform proliferations of endothelial cells mixed with fibrin that interrupt the lumina of arterioles within which they delineate subsidiary channels. Shaw and Ghareeb (1938) first noted them in patients with schistosomiasis and, when prominent and numerous, referred to them as angiomatoid lesions. These channels may extend beyond the adventitia of the original vessels and are in continuity with tortuous labyrinths of large, thin-walled vessels which surround the obstructed arteriole and contribute to the angiomatoid ap-

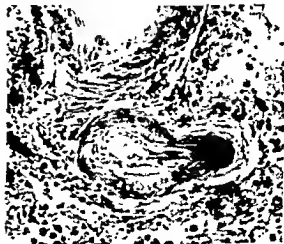


Figure XV-22. Necrosis of muscle and fibrinoid changes in pulmonary arteriole from a 39-year-old woman with primary pulmonary hypertension. Masson's trichrome stain. X 175.

pearance (Figures XV-15 and 29 to 34). Proximally to the interruption, the arteriole is usually greatly thickened by muscular, elastic and intimal changes, but distally it is remarkably thin and large, as in post-stenotic dilatation (Figures XV-30 and 31). This appearance suggests that the pressure in the distal segments is not elevated, and this is confirmed by the absence of congestive changes in the walls of alveoli, such as are noted in mitral stenosis. Masses of blood platelets (Figures XV-35 and 36) may be sequestered within the expanded vessels just beyond the obstruction. The organization of such masses contributes to the development of the granulation tissue.

The nature of the angiomatoid lesions is not entirely clear. In part, they represent organization of thrombi deposited upon the walls of vessels which have become the seat of any of the destructive or exudative lesions that have just been mentioned as the probable consequence of the pulmonary hypertension itself. The localized nature of the obstructing process, and the uniformity in size of the vessels involved suggest that it is non-embolic in nature.

Staemmler and Schmitt (1951), however, have interpreted these lesions as being the result sim-

ply of intimal, chiefly endothelial, proliferation. Some have regarded the angiomatoid lesions as congenital arteriovenous fistulas, or points of connection of pulmonary to bronchial arterioles (Branton, 1950; Froment *et al.*, 1954). It has indeed been theorized that such connections with the systemic circulation could represent the pathogenesis of primary hypertension. In view of their occurrence in secondary pulmonary hypertension, as in schistosomiasis of the lung or interventricular septal defect, it is more reasonable to regard these "plexiform" or "angiomatoid" lesions as acquired. They may be prominent in primary pulmonary hypertension (Kuda *et al.*, 1957; Hufner and McNicol, 1958). Serial sections made by several observers (*e.g.*, Brewer, 1955) have revealed no regular connection with pre existing veins, although occasional minute draining channels may be observed to lead into pulmonary venules. This is to be expected in the drainage of granulation tissue, and should be looked upon as an acquired rather than a congenital state. The dilated thin-walled channels, when traced distally, become distributed into capillaries (Figure XV-31). In addition, vessels penetrating the original adventitia do represent, in some instances, bronchial arterioles, which are known to make a contribution to the capillary components of granulation tissue in the lung (Figures XV-29 and 30). They are related to tortuous channels in the walls of adjacent brouchioles

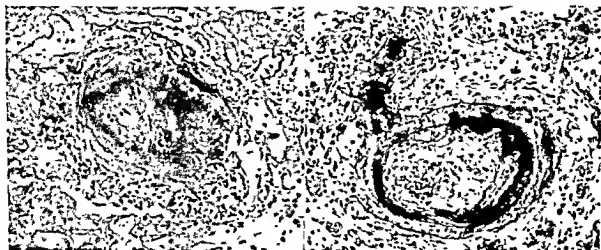


Figure XV-23 (left). Necrosis and massive fibrinoid change of wall of pulmonary arteriole from middle-aged man with long-standing mitral stenosis. There is a polymorphonuclear leukocytic exudate throughout the vessel and in the surrounding edematous connective tissue. (Professor A. C. Lendrum's case, 1956, illustrated with his permission, as are also Figures XV-24 to 26.) Lendrum's picro-Mallory stain. X 190.

Figure XV-24 (right). A larger arteriole with focal necrosis of the hypertrophied muscle layer and loss of portions of the internal and external elastic lamella. Fibrinoid material concentrated in the vicinity of the elastic lamellae, especially the inner. Figure XV-23 is from the same patient. Lendrum's orcein hematoxylin phloxine tartrazine. X 75.

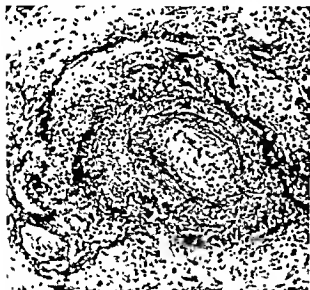


Figure XV-25. Necrotizing arteritis and periaortitis with fibrinoid changes. Figures XV-23 and 24 are also from this patient. Lendrum's orcein-celestine blue-hematoxylin-van Gieson stain. X 120.

that have the position of bronchial rather than pulmonary vessels (Figure XV-32). Studies of injected specimens indicate that they develop in pulmonary hypertension *after* occlusion of pulmonary arterioles has taken place (Figure XV-37). Their presence should also, therefore, be regarded as favoring an acquired state. Extension of the proliferating mass of the granulation tissue beyond the original wall is explained by the defects produced by the previous necrotizing arteritis and by the vascular connections just described. The exact reasons for the exuberant nature of the process in these peripheral pulmonary arterioles is unknown. It is interesting that a similar exuberance can, however, be observed in the organization of necrotic tumor emboli in the pulmonary arterioles.

It may be considered whether some of the distal thin-walled channels represent newly developed branches that connect one pulmonary arteriole to another. Pulmonary vessels do not usually serve as collaterals to one another. Such an interpretation, however, has been placed on terminal vessels in "solitary pulmonary hypertension" that appear to join adjacent pulmonary arteries, by Evans, Short and Bedford (1957) on the basis of their radiographic technique. In casts of lungs from secondary hypertension associated with common ventricle (Figure XV-37 and one other instance), however, such vessels can be traced in continuity with expanded bronchial arteries. The latter characteristically form plexuses that anastomose with more than one pul-

monary artery and they are also in continuity with systemic arterioles in the pleura. The continuity and third dimension provided by the casts reveals these vessels to better advantage than radiographic methods.

Some tentative conclusions regarding the angiomatoid lesions may be drawn: (1) They consist in part of organization-tissue which occludes previously damaged vessels; (2) there may be a contribution of bronchial arterial collaterals that penetrate the original wall from without to participate in the organizing process; (3) branches beyond the occlusion tend to become thin-walled and dilated; (4) it is unknown whether newly formed interpulmonary arterial collaterals, as distinct from bronchial arterial collaterals, are also established, but this seems unlikely.

Tortuosity of Pulmonary Vessels in Hypertension. As in the peripheral vessels, pulmonary arteries subjected to extreme elevations of pressure tend to become tortuous. The actual pressure levels at which this transformation becomes evident are lower than in the systemic circulation. These changes are observed both in primary as well as in secondary hypertension. They are even demonstra-



Figure XV-26. Necrotizing arteritis involving a much larger vessel than in Figure XV-25, but from the same patient. Concentration of fibrinoid material in the region of the external elastic lamella is evident. Lendrum's picro-Mallory stain. X 120.

ble in angiograms and are particularly well shown in plastic casts (Figures XV-38 and 39). The tortuosity is greatest in arterioles which then resemble a corkscrew, but even segmental arteries may become contorted in extreme hypertension. Such changes are not necessarily related to the development of collaterals.

Since a large body of evidence exists that pulmonary hypertension of sufficient degree and duration can produce vascular changes, the tendency to perpetuate or even further to increase the hypertension may be suggested in a summarizing chart (Figure XV-40). These changes tend to reduce the total vascular cross-section, either directly or because certain of them favor thrombosis. A reduction

in vascular cross-section, in turn, favors the development of pulmonary hypertension. This must be considered in terms of the large total reserve of the pulmonary vascular bed, and of the existence of such functional variables as cardiac output, vasospasm, and viscosity of the blood.

C. EMBOLISM

The acute effects of massive diffuse arteriolar or capillary embolism have been described earlier as *acute cor pulmonale*. Pulmonary emboli derive predominantly from the veins of the lower extremities and pelvis and are found in as high as 28 per cent of necropsies in adults (Brenner, 1935). Not all of these,



Figure XV-27 (left). Arteriole with necrosis of muscle, polymorphonuclear leukocytic infiltration of wall, and formation of a thrombus in lumen. From a patient who had pulmonary hypertension associated with interatrial septal defect. (See also Figure XV-35). Lendrum's picro-Mallory stain, X 200.

Figure XV-28 (right). Longitudinal section of small artery showing interruption of muscularis (arrow). This outpouching of the wall is interpreted to represent healing of a lesion such as is demonstrated in Figure XV-27. From a patient with a common ventricle. (See also Figures XV-35 to 37.) X 150.



Figure XV-29 (*left*). Angiomatoid lesion. A small artery containing a plexiform mass of small vessels. No organized clot persists at this level. In other vessels, the presence of thrombus suggested that the process was one of organization. Some component vessels appear to penetrate the wall, suggesting drainage of the granulation tissue into pulmonary venules, or origin from the collateral circulation. That such vessels are often remarkably enlarged is suggested by their size relative to the bronchioles that they accompany. The reason for the enlargement of the granulations is not known. Figure XV-13 is from the same patient.

Figure XV-30 (*right*). Angiomatoid lesion demonstrated to interrupt the course of a pulmonary artery. At the left is the thick-walled muscular artery (*P*) that lies proximal to the plexiform mass. The latter appears at a site at which the muscular wall suddenly becomes thin. It forks towards the right into two branches, one of which is met in a fortunate longitudinal section. This distal branch (*D*) is remarkable for its exceedingly thin wall, but it is an artery, not a vein. A reasonable interpretation is that the angiomatoid mass represents organization of the thrombus that arose in a region in which the muscular wall of *P* is now thin (formerly necrotic?). The thick wall of *P* reflects the high pressure proximally, the pressure in the thin-walled segment probably was low. At the arrow is a vessel penetrating from without, and probably a branch of a collateral arteriole. Figures XV-13 and 29 are from the same patient. X 55.

however, are associated with infarction of the lung. Parker and Smith (1938) have reviewed the mechanisms that may be concerned. When the right side of the heart becomes dilated in failure, mural thrombi are frequently formed, especially in the auricular appendage, whence emboli may arise.

Multiple or repeated embolism of the larger pulmonary arteries can lead to right cardiac failure. This may be immediate but may be preceded by compensation, manifested anatomically in right cardiac hypertrophy.

Clinical and anatomic features have been reviewed by Castleman and Bland (1946), Carrol (1950) and Hollister and Cull (1956). Subtotal or even total occlusion of the trunk and main branches of the pulmonary artery has been described (Tulpius, 1641; Hart, 1905; Stadelmann, 1909). In these instances it is probable that the embolism of the main branches occurred *seriatim*, with sufficient time for recanalization to take place within one main branch before occlusion of the other.

It has also been suggested that multiple emboli

may become organized to a state that is easily confused with "pulmonary arteriosclerosis." This, in fact, was the original stimulus to C. V. Harrison's (1948) experimental work. Recent observations by Thomas and his associates (1956) support this view.

It is probable that embolism frequently is a contributory factor superimposed upon others in the genesis of pulmonary hypertension. On the contrary, if hypertension is the consequence primarily of embolic phenomena, vascular lesions of the type described in the previous sections may be superimposed and vicious cycles may thus be initiated (Figure XV-30). Tumor emboli may also lead to the development of cor pulmonale. Carcinoma of the stomach, more than any other type of tumor, is likely to metastasize in this fashion (Greenspan, 1934; Spain and Handler, 1946; Morgan, 1949; Storstein, 1951). Ultimate organization of tumor emboli to yield an appearance similar to "sclerosis" has been described by Saphir (1947).

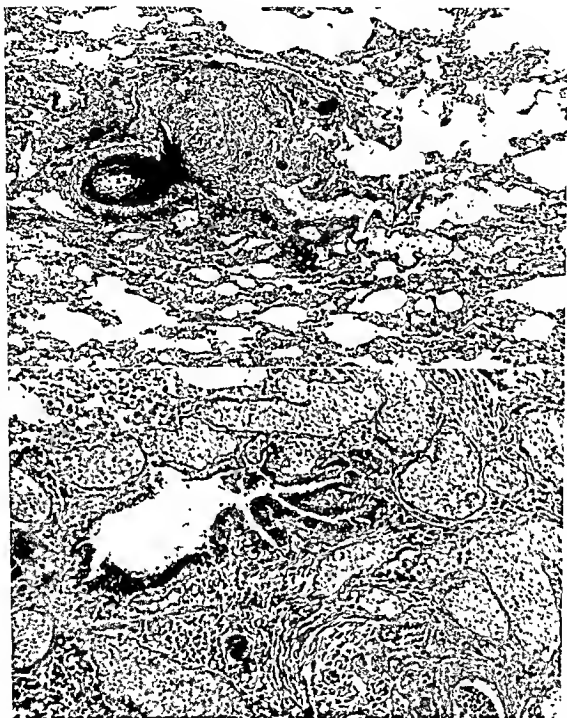


Figure XV-31 (*upper*). Angiomatoid lesion in schistosomiasis. Lung of a 24-year-old Puerto Rican woman who had been living in the United States for 5 years before her death shortly after delivering a child. At the left is a thick-walled muscular artery with concentric fibrinoid deposits in the intima, continuous with an obstructing mass of granulation tissue where the wall is destroyed. A widely patent, but thin-walled, channel proceeds to the right from the granulation tissue and becomes distributed to capillary channels. The similarity to the relationship demonstrated in Figure XV-30 is striking, despite the different etiology of the pulmonary hypertension. X 30. (Courtesy of Dr. Nilo Herrera.)

Figure XV-32 (*lower*). Angiomatoid lesion from same patient as in Figure XV-31. At the right below is the remnant of a pulmonary arteriole filled with an angiomatoid mass. The thin-walled channels in the wall of the adjacent bronchiole have the distribution of bronchial vessels, and are in continuity with those that penetrate the adventitia to become merged with the plexiform mass near the center of the pulmonary arteriole. X 125.



Figure XV-33 (*upper*). Angiomatoid lesion. (Figure XV-31 is from same patient.) A mass of thin-walled vessels is associated with an arteriole obstructed by a granulomatous response to an egg. (Compare with Figure XV-34.)

Figure XV-34 (*lower*). Angiomatoid lesion (higher magnification of Figure XV-33). At the right within an obstructed pulmonary artery is seen a well preserved schistosome egg. Recanalizing channels near the egg contain murally deposited hyaline acidophilic material. At the left are the thin-walled component channels of the angiomatoid mass, X 125.



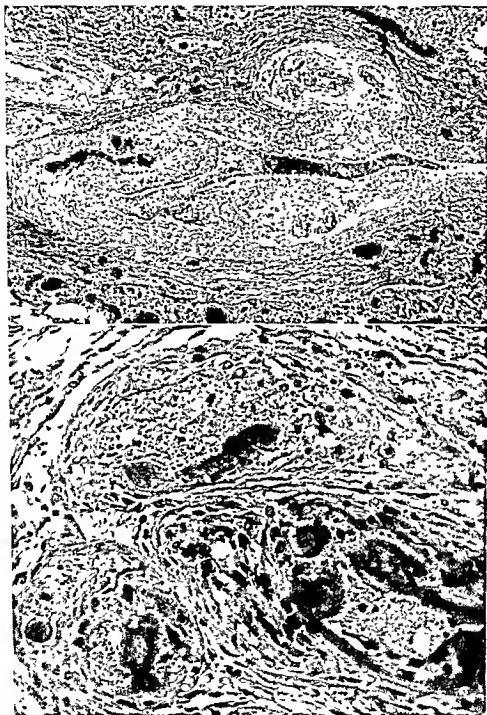


Figure XV-33 (upper). "Platelet sequestration" and other changes in common ventricle (from same patient as Figures XV-27 and 28). A large artery with a markedly thickened wall (organizing and partly recanalized thrombus?). A small branch extends upwards and is the seat of an angiomatoid lesion demonstrated under higher magnification in Figure XV-36. X 42.

Figure XV-36 (lower). Angiomatoid lesion seen in right upper portion of Figure XV-35, under higher magnification. Clumped platelets and fragments of fibrin and proliferated endothelial cells within thin-walled vessels. X 320.

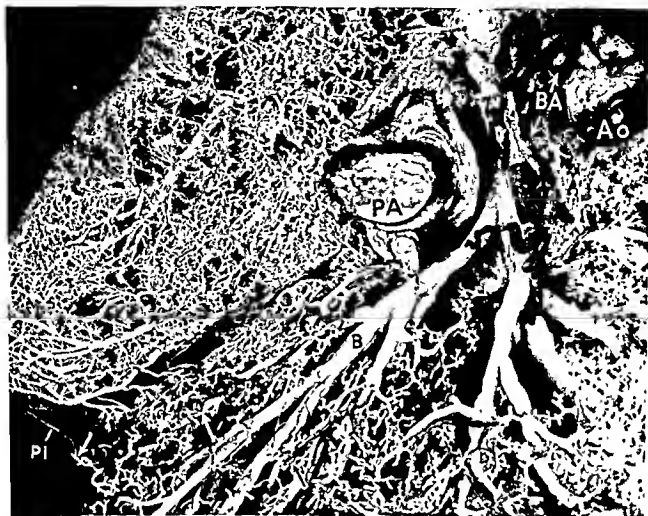


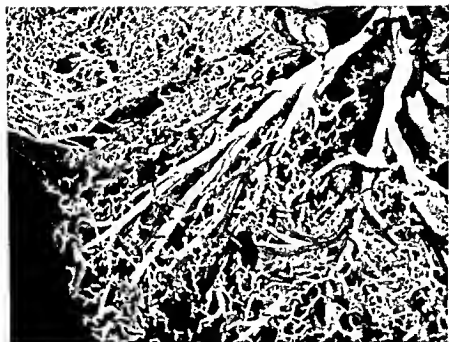
Figure XV-37 Bronchial arterial enlargement and other changes associated with pulmonary arterial occlusive disease in common ventricle (as illustrated in Figures XV-15 to 18, 28, 35 and 36). The aorta (Ao) gives rise to greatly enlarged bronchial arteries (BA). The latter connect with the pulmonary vessels where these have become extremely tortuous (arrows) and some bronchial arterioles are continuous with a plexus in the pleura (PI). In histologic section, such regions of anastomosis are revealed occasionally as components of the angiomatoid lesions. Enlarged proliferated bronchial arteries can be seen along the medial basal segmental bronchus (B). The transected main trunk of the right pulmonary artery is identified by the label PA.

Barnard's (1957) demonstration in rabbits that repeated intravenous injections of small quantities of oxygen, nitrogen or argon can produce striking pulmonary vascular lesions is of great interest and warrants further study.

Schistosomiasis is an important cause of obstruction of the pulmonary vessels in some parts of the world (Shaw and Ghareeb, 1938; Bedford *et al.*, 1946; Marchand *et al.*, 1957). The eggs are swept into small pulmonary arterioles which become the seat of a destructive arteritis and periarteritis probably associated with allergy. Thrombosis complicates this condition. Effects of hypertension are evident

in muscular thickening and other changes in the pulmonary vessels proximal to the obstruction. The "angiomatoid" lesions, at one time thought to be specific for this condition, are now known to be related to vascular obstruction and pulmonary arterial hypertension *per se* (Figures XV-31 to 34).

Because so many of the patients with primary hypertension are young married women (Heath *et al.*, 1957; Shepherd *et al.*, 1957), the question is pertinent whether amniotic fluid embolism may not be the initiating phenomenon. It is possible that considerable embolization of this sort can take place without production of the syndrome of shock or of acute cor pulmonale that has fre-



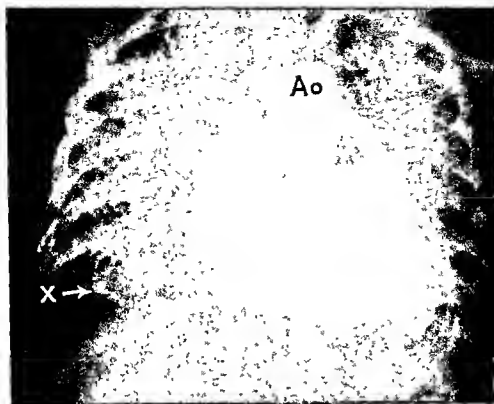


Figure XV-38 Tortuosity of pulmonary arteries in pulmonary hypertension (from patient with primary hypertension, see Figure XV-21). Film taken 8.4 seconds after injection of the radio-opaque medium. Note tortuous pulmonary arteries, one of which, in the region of the middle lobe, is indicated by an arrow and the symbol X. There is delay in transit of blood through the lungs as indicated by persistence of visibility of the pulmonary arteries and of components of the spinovertebral venous plexus, at a time when the aorta (Ao) is already opacified.

quently accompanied the process when fatal. Moreover, the difficulty of demonstrating the particulate components of this fluid are well known, and they must be sought by appropriate methods (Attwood, 1956, 1958).

In summary, embolism can contribute to cardiopulmonary disease, perhaps to a larger degree than has been thought. Further study is needed.

D. COMPRESSION

Obliteration of vessels by external compression may occur in primary or metastatic neoplasms. This process may also be diffuse as a consequence of perivascular lymphatic metastasis.

The effects of compressive atelectasis, although usually insufficient to interrupt completely the blood flow through a lung, may increase resistance to the output of the right ventricle. This is discussed elsewhere. Such a result may be observed in deformities of the chest, or when the

lung is collapsed by fluid, air or tumor in the pleural space.

Compression of minute vessels within distal air passages may also result from focal air-trapping, as in broncho-obstructive disease.

E. LOSS OF CAPILLARIES

Hardly a tissue in the body is more vascular than the wall of the alveolus, and this has been well demonstrated anatomically by Miller (1937). It has come to be presumed that there is a loss of considerable portions of this bed in fibrosis or emphysema. This is certainly true when large masses of alveoli are replaced by hyaline connective tissue, or by bullous transformation. The earlier phases of this process, however, are more difficult to assess quantitatively.

The relative vascularity and resistance of fresh granulation tissue as compared with normal alveolar substance has not been accurately determined; nor has the source of new

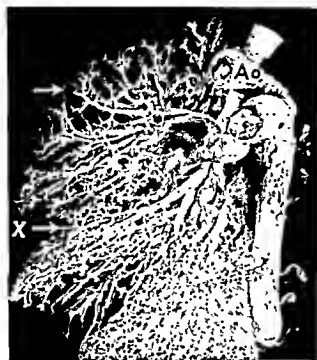


Figure XV-39. Tortuous vessels (arrows) as demonstrated in the cast of the right lung of patient whose angiogram is illustrated in Figure XV-38. Arrows indicate the attenuated and markedly tortuous vessels in the periphery of the lung, one of which probably corresponds to the vessel marked X in the angiogram.

capillaries in the former been established. There is evidence that at least a portion of these capillaries come from bronchial arteries and that the total resistance in the granulation tissue is probably relatively high.

In emphysema, there is a loss of vascularity that involves not only capillaries, but also vessels of much larger size. This process, which is not well understood, is discussed in the third part of this chapter.

In sum, although loss of capillaries and small vessels in general may ultimately come to be a matter of first importance, its quantitative, functional and anatomic definition is difficult and must be considered in relation to other processes, such as spasm, development of anastomoses between systemic and pulmonary arteries, and immobilization of the lung.

II. Increased Postcapillary Resistance

Acute effects of increased resistance to outflow from the pulmonary capillaries have been discussed in Part 1 of this chapter, and the more chronic effects are considered in Part 3, with reference to mitral stenosis.

III. Development of Shunts: Bronchial Arteries to Pulmonary Arteries

In many types of fibrosing pulmonary disease, and especially in bronchiectasis, there is a great expansion of the bronchial arterial collateral circulation, and large precapillary anastomoses of these vessels with the pulmonary arteries can easily be demonstrated (Wood and Miller, 1938; Liebow *et al.*, 1949, 1950b; Latarjet, 1954). The pulmonary arteries themselves may become decreased in size.

Since each of these anastomoses represents a connection with the high-pressure aortic circulation, it must represent a point of increased peripheral resistance. The effect is to shunt blood away from the diseased tissue within which the anastomoses occur to normal parenchyma where gas exchange can take place. Their presence helps to account for the lack of desaturation of systemic arterial blood, even when large masses of pulmonary substance are involved in bronchiectasis or other fibrosing disease (Liebow *et al.*, 1950b). Other contributory factors in this shunting mechanism are partial obliteration of the pre-existing pulmonary capillary bed and interference by fibrosis or pleural thickening with the blood-pumping action of the thorax. Neither of the latter is, however, sufficient in itself to insure the shunt (Rosenberg, 1952).

In massive unilateral pulmonary disease, the shunting effect can involve an entire lung and this can clearly be demonstrated by angiography. When radio-opaque material is introduced into the right side of the heart, it enters only the pulmonary artery of the normal lung, despite the patency of both pulmonary arteries. This patency can subsequently be confirmed in the resected diseased tissue.

That a reversal of flow in the pulmonary artery of the diseased side toward the hilum can take place was first demonstrated by catheterization in 1950, in a patient with bronchiectasis involving all segments of the left lung (Figures XV-41 to 45) (Liebow *et al.*, 1950b).

A catheter introduced into the left pulmonary artery received without suction fully oxygenated

blood. This blood flowed from the aorta and bronchial arteries by way of the communications with the pulmonary arteries, proximally, against the usual direction of flow. This was subsequently confirmed on a segmental basis by Roosenburg and Deenstra (1954). In this demonstration, obstruction of a pulmonary artery by "jamming" the catheter must not be permitted to occur, since this will abolish the counter-pressure from the proximal end that is normally present and, therefore, may cause blood from the collaterals to flow toward the catheter, whether or not this was the case in the unobstructed vessel.

Additional confirmation has come from the study of another patient by Alley and associates (1958) in whom contrast medium introduced high into the descending thoracic aorta opacified the enormously enlarged tortuous bronchial vessels of a diseased left lung and then, in *retrograde* direction from these vessels, the pulmonary artery.

Although there is no doubt of the existence of large anastomoses in some of these patients, it is obvious that the direction of flow depends upon the relative pressure on the two sides of the anastomosis, which is not necessarily constant. For example, if a sufficient rise in the pulmonary arterial pressure occurs late, when disease has become sufficiently diffuse, there may be a reversal once again with a peripheral flow in the pulmonary artery into the capillaries and veins of the diseased side. When sufficiently numerous, these points of increased resistance doubtless contribute to the development of pulmonary hypertension, irrespective of the direction of flow. They are unlikely alone to be responsible for pulmonary hypertension unless a volume

of parenchyma greater than that of one lung is involved in disease.

IV. Decreased Efficiency of Respiratory Blood Pump

There is some suggestion that insufficient attention has been paid to the assistance rendered by the respiratory movements of the chest to the right side of the heart in its blood-pumping function, as early emphasized by Costa (1928). In the normal lung, the elastic tissue is constantly on a stretch and the stretching is increased during the inspiratory movement. During inspiration, therefore, a greater expansile traction is exerted on all structures within the lung, including the vessels to which the elastic tissue is attached. The inspiratory movement, consequently, tends to enlarge the vessels, and this can be accomplished only by an intake of blood. Forward flow is, of course, insured by the direction of the cardiac valves and the action of the heart. During the expiratory phase, the elastic traction is diminished and tonic recoil of the vessels tends to empty them (Figure XV-46). This pumping is reduced or abolished if the lung tissue is partly or totally immobilized, as by dense pleural fibrosis. Relative immobilization can also result from bronchial obstruction with either atelectasis or air-trapping; paralysis, or other interference with the movements of the diaphragm and intercostal muscles; pneumothorax; filling of the alveoli with exudate, as in acute pneumonia or pulmonary edema; interstitial emphysema; pleural thickening; or compressive atelectasis, as by pleural exudates or tumors.

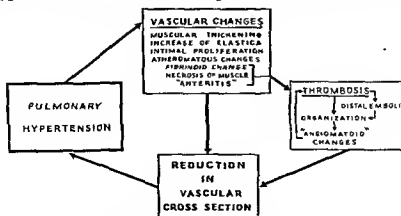


Figure XV-40. Vicious cycles involved in possible perpetuation and increase of pulmonary hypertension.



Figure XV-41 (*upper*). Bronchogram made in November, 1943, demonstrating bronchiectasis involving all segments of the left lung. The right lung is over-expanded in consequence of shift of the mediastinum to the diseased side. The patient was a 32-year-old man whose disease began after aspiration of a tack 25 years previously.

Figure XV-42 (*lower*). Circulation in bronchiectasis. Angiogram made in 1949 from same patient as in Figure XV-41 demonstrating that only the vessels of the normal right side are opacified, and that blood is shunted away from the left pulmonary artery, or is flowing in reverse towards the hilum. This interpretation is confirmed by results of catheterization (see text).

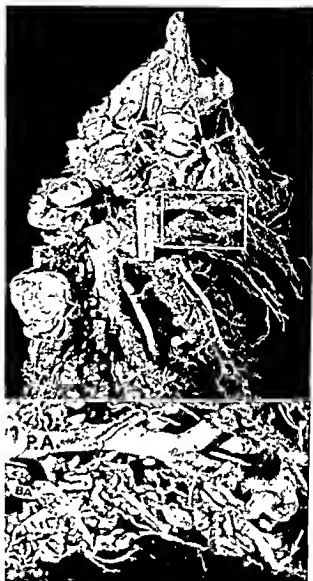


Figure XV-43 (*upper*). Cast of the left lung (Figures XV-41 and 42 are from the same patient) demonstrating the patency of the pulmonary artery and its anastomosis with a greatly expanded plexus of bronchial arteries. The field outlined in white is shown in close-up in Figure XV-44.

Figure XV-44 (*lower*). Detail of an anastomotic channel (arrow) approximately 1 mm. in diameter, connecting a pulmonary artery (PA) and a branch of a large bronchial arterial plexus (BA). Fully saturated blood from the aorta entered the lung by way of the bronchial arterial plexus and traversed the channel to pass to the pulmonary artery. Within the pulmonary artery some of the blood was demonstrated to flow in reverse of the usual direction; the remainder entered the capillaries of the fibrotic lung and was delivered into the draining veins.

When only a part of the lung is involved in any of these processes, blood is diverted to those parts of the parenchyma where pumping is still effective. In fact, compensatory mechanisms involved in assuring an adequate air-exchange tend to increase the pumping action within the uninvolved pulmonary tissue.

This shunting mechanism has been demonstrated for a whole lung by Bjork and Salen (1950,) by Peters and Roos (1952), and by Rosenberg (1952). Rosenberg has shown that simple immobilization of a lung by enshrouding it in cotton mesh does not completely prevent the inflow of blood as demonstrated angiographically, although the blood flow is markedly reduced in contrast with that to the normal lung.

In pulmonary emphysema, the total pumping action may be reduced, in part by bronchial obstruction with air-trapping and consequent immobilization of portions of the parenchyma, in part from a quantitative restriction in the total elastic tissue, in part perhaps from a qualitative alteration of this substance. The analogy is to an old garter, the stretching of which involves little pull or counterpull.

V. Increased Blood Viscosity

When the systemic arterial oxygen tension is diminished, there is a stimulus to polycythemia, the viscosity of the blood is increased, and with it the work of the heart.

VI. Increased Flow

In normal man, a three- to four-fold increase in transpulmonary blood flow above the cardiac index is accommodated by such a diminution of resistance that there is no increase in pulmonary arterial pressure. In chronic pulmonary disease, however, as resistance (R) rises, it is obvious from the formula $P = kFR$ that the pulmonary arterio-venous pressure gradient (P) will rise for constant flow (F); viscosity is assumed to be constant. Moreover, an elevated pressure tends, in itself, to produce further damage to vessels with additional increment in resistance, as has been described.

Inefficient ventilation in chronic pulmonary disease may lead to a decrease in oxygen ten-

sion that initiates mechanisms tending to increase cardiac output. With the associated polycythemia, moreover, the blood volume and venous pressure tend to rise. The expanded output is flung against a resistance increased by anoxia-induced vascular spasm and, in varying degree, by physical loss or obstruction of the peripheral vascular bed.

Flow in the pulmonary vascular bed may also be increased as a result of various congenital malformations. Left-to-right shunts in patent foramen ovale, septal defects, common ventricle, and other malformations, may involve large increases in blood flow through

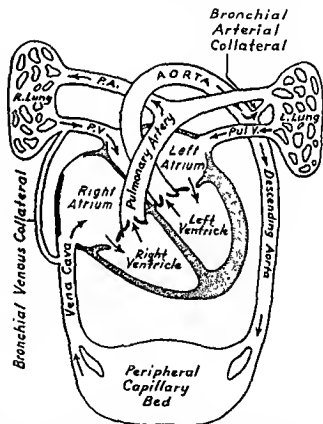


Figure XV-45. Schema of the course of the circulation when an extensive collateral circulation has developed, as suggested by the observations of Figures XV-42 to 44 in a patient with chronic fibrosing pulmonary disease (bronchiectasis) involving all segments of the left side. The collateral branches from the aorta are indicated as a single trunk distributing its blood through the anastomotic channel into the pulmonary artery. Some blood is impelled by the higher pressure in the collateral channels and the greater peripheral resistance in the diseased lung to flow, in reverse, toward the hilum; some may be distributed through the remaining capillaries to be recirculated to the left side of the heart; this latter flow is a burden solely upon the left side of the heart. (Figures XV-41 to 44 from Liebow *et al.*, 1950a.)

the lungs. Drainage of one lung into the right side of the heart or its major tributaries, when occurring as an isolated anomaly, is usually well tolerated by the other lung. Less in the way of quantitative data is available regarding pulmonary blood flow in such anomalies as common ventricle, aortic atresia, or the infantile type of coarctation, where the right ventricle performs the work of a systemic ventricle or the pulmonary arteries are subjected to systemic pressure. Under these circumstances, there is usually a high pulmonary arteriolar resistance, and there may also be a large flow. It is remarkable that patients with truncus arteriosus may survive into adulthood with little evidence of disability (Christeller, 1916-18).

3. PATHOGENETIC FACTORS IN SOME TYPES OF COR PULMONALE

It may be of interest to consider the interplay of the various mechanisms just discussed in a number of conditions to which the term *cordipulmonary* may be applied. Some of these are selected from a list of diseases associated with cor pulmonale (Table XV-3).

This list varies depending upon definitions and in part on the population from which the material is drawn. Emphysema is outstanding, and bronchiectasis in most listings is perhaps second, although far behind the first.

TABLE XV-3
Diseases Associated with Cor Pulmonale
(Based on Autopsy Material)

	Scott and Garcin (1941)	Spain and Handler (1946)	Spatt and Grayzel (1948)	McKeown (1952)
Emphysema	32*	40	29	39
Bronchiectasis		6	7	17
Asthma . . .		6		14
Silicosis . .	12	2		
Tuberculosis	1	2	3	7
Thrombi or emboli		1		5
Metastatic carcinoma			2	
Arteriolar sclerosis . .		1	1	4
"Fibrosis" . .	1			7
Kyphoscoliosis		1		3
Unknown . .				4

* The digits in the table indicate numbers of patients.

The parameters of flow and pressure have usually been measured at rest and flows as large as 8 liters or even more per square meter of body surface per minute, e.g., in patent ductus arteriosus, may occur at normal pulmonary arterial pressure. Ultimately, vascular changes take place and these are sometimes extreme and not different from those to be seen in primary pulmonary hypertension.

Exactly how these changes are produced is a matter for conjecture at the present time. It may be that they result from episodic sharp rises in pulmonary arterial blood pressure, occasioned by torrential increases in blood flow upon stress, or by increased resistance from arteriolar spasm, or possibly by other means even less well understood.

Data from Griggs and associates (1939) are similar, although recorded in a somewhat different way. Kyphoscoliosis will be analyzed, although it is uncommon; when it does occur in severe form, it is ultimately often associated with cor pulmonale. Finally, mitral stenosis will be discussed as an example of a cardiac condition with important pulmonary complications. Each of these will be briefly outlined within the framework constructed in the preceding sections.

TABLE XV-4
Pathogenetic Factors in Emphysema

- I. Traction
 - A. "Compensatory" to
 1. Atelectasis
 2. Fibrosis
 3. Surgical ablation of lung tissue
 - B. To enlargement of the thorax
- II. Obstruction of air passages (diffuse or focal) by
 - A. Mucus
 - B. Muscle spasm
 - C. Muscle hyperplasia (?)
 - D. Fibrosis of bronchioles
 1. Mural
 2. Intraluminal
 - E. By stretching and distortion as bullae enlarge
- III. Destruction by
 - A. Necrosis or atrophy
 - B. Tension beyond obstruction (?)
- IV. "Loss of elasticity" (?)

Pulmonary Emphysema

For present purposes, pulmonary emphysema will be defined as any condition with persistent hyperexpansion of distal air spaces. An attempt at logical discussion, however, is plagued by uncertainties of usage, by lack of knowledge regarding the pathogenesis in the individual case, and by the difficulties in determining the extent of the process and of co-existing lesions such as pulmonary fibrosis (Kountz and Alexander, 1934; West *et al.*, 1951; Ebert, 1956). It is certain, however, that a relatively slight degree of diffuse emphysema, especially if there is a factor of obstruction of the bronchioles, is enormously more significant functionally than an anatomically impressive but focal bullous form (Spain and Handler, 1946, Gough *et al.*, 1952). Bullae may, however, become important if they are large enough to compress normal parenchyma.

Some diverse pathogenetic factors may be listed, and these can be only briefly discussed (Table XV-4).

I. TRACTION

Atelectasis or fibrosis of one part of the lung is compensated in other parts by over-

expansion, chiefly of the distal air spaces, except insofar as there is a change in the total capacity of the thorax. Since the latter is relatively fixed, emphysema represents by far the major part of the spatial rearrangement. Traction, rather than obstruction, appears to be the mechanism of the early focal emphysema of coal miners (Heppleston, 1947).

There are some who believe that an increase in the capacity of the thorax, that occurs in part as a result of changes in the joints of the spine, is a common mechanism in the genesis of emphysema. This position has been taken by Loeschcke (1921, 1928) and his reasons have been clearly stated and well illustrated. It may, however, be asked with justice whether the enlargement of the thorax is not an effect of emphysema, especially of the obstructive type.

II. OBSTRUCTION OF BRONCHIOLES

Perhaps the most important mechanism in the genesis of emphysema is obstruction of distal air passages, with air-trapping (Figures XV-47 and 48). Air-trapping is easily demonstrable in spiograms. Functional evidence regarding the mechanism and significance of inadequate ventilation has been presented (West *et al.*, 1951, Fry *et al.*, 1954). Blocking of bronchioles by mucus or exudate

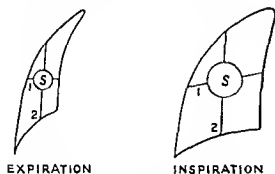


Figure XV-46 Pumping effect of respiratory movements. In this schema, the lung is conceived to consist of elastic fibers (e.g., 1 and 2) that are always on stretch; therefore, they exert a pull against the walls of any structure such as a vessel (S). With inspiration, the pull becomes greater with a tendency to enlarge S. Since the vessels are filled with blood, an indistensible fluid, this enlargement can occur only by greater filling; hence, by the pumping action of the respiratory movements, the lungs serve as an "accessory heart."



Figure XV-47. Portion of cast of distal distribution of respiratory tree in emphysema. Just beyond a rapidly tapering bronchiole there is expansion into a labyrinth of air passages which are greatly distended, presumably because of air-trapping. X 2.



Figure XV-48. Air-trapping in consequence of a vicious cycle operating in bullous emphysema. As the bullae expand, the bronchioles are thereby displaced and stretched, and suffer a reduction of lumen with a consequent greater tendency to air-trapping, thus, further growth of the vesicles occurs. Some of the bullae have been removed from this cast to demonstrate such a bronchiole (arrow). The vessels are affected by similar process and by other changes (Slightly reduced.)

is most important during infections of the respiratory tract and may be reversible, although it is often persistent and recurrent. Much remains to be learned regarding factors, including familial, that govern the nature and viscosity of "mucus." Bronchitis and bronchiolitis and even pneumonitis frequently precede and accompany pulmonary emphysema. Little understood also is the role of the musculature in emphysema (Figures XV-50 and 51) which may be notably increased in such distal distribution as the walls of the respiratory bronchioles and alveolar ducts (Loeschke, 1921). This muscle may also become abundant in the walls of the bullae, even in subpleural position (Liebow *et al.*, 1953). The presence of muscle and its capacity for

spasm contribute to anoxia, but account for the beneficial effects of broncho-dilator drugs in some patients with obstructive emphysema.

The frequent presence of fibrosis (Figure XV-49) with consequent rigidity and inexpandibility of the walls of the bronchioles has been described by Amberson and Spain (1947) and by Spain and Kaufman (1953). Fleischner (1950) has stressed the increment in resistance to air flow that occurs simply from the diminution in diameter of small bronchioles. Functional studies of the enormous increase in pressure necessary to secure air flow, especially during expiration, in some subjects with emphysema have been reported by Fry and associates (1954).

III. DESTRUCTION

Direct necrosis of alveolar septa with conse-

quent fusion of adjacent alveoli does not appear to be an important mechanism in the genesis of chronic emphysema. A more subtle atrophy of portions of alveolar walls with the development of pores that enlarge and create a confluence of air spaces has, however, been described. Orsós (1907) thought this process involved previously intact walls, whereas Sudsuki (1899) described it as an enlargement of the pores of Cohn. It may also be questioned whether this process is not the effect of the gaseous tension beyond an obstructive lesion which might compress capillaries and thus render the walls of distal air spaces anemic. Whether there is actually tearing of alveoli has been questioned by Hartroft (1945), who indicated how histologic appearances suggesting tearing might be produced simply from the distention of the distal air spaces. It appears probable that both factors are at work in the emphysematous lung with the result that like the chambered Nautilus, it comes to consist of more and more stately mansions. This process of continuous fusion of distal air passages has been well described by Loeschcke (1921, 1923).

IV. LOSS OF ELASTICITY

Much has been written, but little proof has been advanced that there is a truly qualitative change in the elastic substance of the lung in emphysema. It is true that the total tendency of the lung to collapse and, therefore, the inward pull on the thoracic cage, may be reduced in emphysema. This may mean that some parts are overdistended by trapped air and, therefore, have the effect of space-occupying lesions. The pull may also be lessened, and intrapleural pressure thereby raised, by physical loss of elastic substance,—a quantitative, rather than a qualitative effect.

From this analysis it appears that emphysema associated with obstruction of bronchioles has the greatest functional importance. Only when extremely extensive will the other forms be significant clinically, although they coexist with obstructive emphysema.

Vascular Changes in Emphysema. It must be admitted that attempts to correlate the parenchymal and vascular changes in pulmonary emphysema have not been particularly

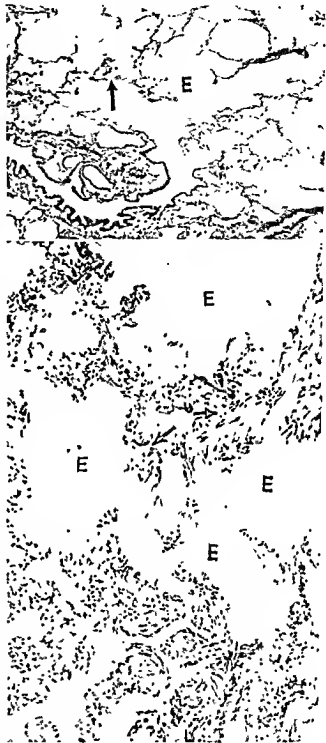


Figure XV-49 (top). Early phase of emphysema. Beyond the thickened and narrowed bronchiole, there is overexpansion of the distal air passages (E). Inter-alveolar septa are thin. Gaps appear in the latter (arrow) to join adjacent emphysematous alveoli in their peripheral distributions. X 40.

Figure XV-50 (middle). Muscular hyperplasia in respiratory bronchioles and alveolar ducts in emphysema with narrowing proximal to emphysematous vesicles (E); gaps corresponding to the canals of Lambert are apparent (arrows). X 150.

Figure XV-51 (bottom). "Knobs" of muscle in narrow distal air passages leading to emphysematous bullae (E). X 150.



Figure XV-52 (upper). Vascular changes in bullous emphysema. The walls of the vessels are remarkably thick and the lumina narrowed to the point of obliteration in some instances. For details see Figure XV-53. These vessels traverse or lie in the wall of a large bulla. This is a focal change associated with the bullous transformation and is not indicative of diffuse pulmonary vascular disease. X 30.

Figure XV-53 (lower). Detail of Figure XV-52, demonstrating that the thickening is largely the consequence of muscular hyperplasia and hypertrophy. The muscle is arranged in layers, some of which are longitudinal and chiefly intimal, and some circular and in the position of the media. X 120.

successful. Decrease in apparent vascularity of alveoli in this condition was noted early by Isaaksohn (1871), and his observations were confirmed by Sudsuki (1899), Orsós (1907) and others. As the bullous transformation progresses, devascularization becomes increasingly obvious. Although it has been de-

nied that the alveoli "rupture," they ultimately disappear, subtly but certainly. It may also be questioned whether increased intra-alveolar tension is a factor in the obliteration of minute vessels. On the contrary, some have postulated that the initial event is the loss of the vessels, perhaps even those derived from the systemic arterial side (Cudkowiec and Armstrong, 1953). What is needed is knowledge of which comes first, and present indications are that it is the parenchymal, rather than the vascular changes. Other observers have found an increase in collateral arterial blood supply in emphysema (Marchand *et al.*, 1950, Liebow, 1953), but this may be determined in part by the extent of such "associated" lesions as fibrosis and bronchiectasis. The expansion of the bronchial veins and its possible significance have been discussed in the first section of this chapter.

The residual skeleton of larger vessels is remarkable for its immense mass of muscle, and these vessels may come to be totally obliterated by the effects of muscular hyperplasia (Figures XV-52 and 53). Since this obliterative process may be a focal change, confined to a few bullae, the peripheral resistance may not be measurably increased by this alone. Other arterioles exhibit restriction of the lumen by various other types of "sclerotic" changes. Parker (1940), in particular, has stressed their focal nature. Actually such changes may be indicative simply of an obliteration of the distal vascular bed. Some appear to be of thromboembolic origin (Kernen *et al.*, 1958). The necessity for considering the background of pulmonary vascular lesions to be expected in the absence of hypertension at a particular age has been emphasized by McKeown (1952). She concluded that these were only slightly accentuated by emphysema.

In sum, it appears highly probable that only in rare instances are the irreversible changes in the larger vessels and loss of capillary bed a prime factor in the pathogenesis of pulmonary hypertension in emphysema. This is indicated by the reversibility of the hypertension in many patients with this condition, upon relief of anoxia, in contrast with those in whom there is massive pulmonary

fibrosis, as in silicosis (Harvey *et al.*, 1951; Ferrer and Harvey, 1954).

Since pulmonary arterial hypertension in emphysema is usually mild, necrotizing arterial lesions, "vasculitis" and fibrinoid changes are not commonly found. Even moderate pulmonary hypertension may, however, lead to cor pulmonale.

Diminished Pumping Action of Thorax. When focal air-trapping occurs in emphysema, there is in some patients a decrease in alternating inspiratory stretch and expiratory relaxation of tension upon the pulmonary vessels. In that form of the disease in which giant bullae result from air-trapping, the compressed remaining lung tissue also is effectively immobilized. In others, however, especially if focal fibrosis exists, a contrary effect may be expected, as indicated by large respiratory swings in the intrapleural pressure (Borden *et al.*, 1950a, b, Fry *et al.*, 1954).

Effects of Anoxia. By and large, the greatest functional difficulties appear to arise in the diffuse form, in which obstruction of bronchioles is the dominant factor. Harvey and associates (1951) observed that, when the arterial blood did not become desaturated upon exercise in patients with emphysema, there was usually no pulmonary hypertension. Yu and associates (1953) found that the degree of pulmonary hypertension in general appeared to depend upon the severity of the anoxia and hypercapnia; "capillary" pressure was not elevated. According to Borden and co-workers (1950a, b), the hypertension is usually moderate, the mean ranging from 15 to 37 mm. Hg. Despite the moderate hypertension, right-sided cardiac hypertrophy may be considerable—probably a reflection of the chronicity of the process and its recurrent exacerbations. Abundant evidence now exists that a vasospastic factor, probably induced by anoxia, exists in pulmonary emphysema. This is suggested by the observation that the pulmonary hypertension and congestive heart failure are gradually reversible in many patients upon relief of the bronchiolar obstruction and restoration of more nearly normal alveolar oxygen tensions and systemic oxygen saturation (Harvey *et al.*, 1953). Such a vaso-

spastic factor is frequently superimposed upon a diminished capillary bed and upon at least locally narrowed arteries. Moreover, cardiac output is likely to be high in these individuals (McMichael and Sharpey-Schafer, 1944; see also Harvey *et al.*, 1951).

Bronchiectasis

The mechanism of bronchiectasis appears to be traction accompanying the organization of foci of necrotizing bronchopneumonia. The resulting scars are centered upon bronchioles that often become obliterated (Mallory, 1948, Lindskog and Liebow, 1953). As the scars contract, a pull is exerted upon the more proximal bronchi, which therefore become ectatic, although otherwise relatively intact. These dilated bronchi may be sacs that end more or less blindly. The expanded state of any alveoli beyond them is maintained by "collateral respiration" through the pores of Kohn, from adjacent uninvolved parenchyma.

Bronchiectatic tissue is supplied by vastly expanded bronchial arteries that come freely into communication with the pulmonary arteries. Such anastomoses often have a diameter of 1 mm., and sometimes exceed this size. Their role in shunting blood into more nearly normal parenchyma and in contributing to pulmonary arterial hypertension has been discussed in Part 2 of this chapter.

The conspiring factors in the genesis of the hypertension then, are: (1) a reduction of the capillary bed in consequence of fibrosis, (2) anastomoses between the pulmonary and bronchial arteries, and (3) relative immobility of the involved tissue with decreased efficiency of the blood-pumping action of the respiratory movements.

It must be remembered that bronchiectasis often is associated with pulmonary emphysema and with varying degrees of massive pulmonary fibrosis, often elsewhere than in the involved segments.

Kyphoscoliosis

The high incidence of cor pulmonale in severe kyphoscoliosis is well known (Samuelson, 1952), but the mechanisms concerned are probably not simple. There is inevitably some



Figure XV-54. The thorax in severe kyphoscoliosis. The major changes consist of a great antero-posterior elongation, with narrowing to the point of the gibbus (arrows) and, obviously, marked flaring anteriorly.

distortion of the contents of the thorax. For example, the aorta may become bent at right angles upon itself as it is made to conform to the gibbus. The lungs, indeed, maintain their deformity upon removal from the thorax, but the study of casts, even in extreme instances (Figures XV-54 and 55), demonstrates that the large vessels, at least, accommodate by appropriate foreshortening or elongation without obstructive angulation. In other respects, the casts reflect the appearance presented by sagittal sections of the lungs *in situ* as prepared by Loesche. In the instance illustrated here, the lower lobes are atelectatic as a consequence of confinement in the relatively small pyramidal space at the far postero-inferior angle of the deformed chest. On the contrary, the bulk of the lung consists of the hyperexpanded upper lobes. In part, the emphysema is, therefore, of an extreme "traction" type. In addition to the fibrous, or active, residua of tuberculosis that may be common to both the spine and lungs, patients with kyphoscoliosis are also known to be subject to frequent bronchopulmonary infections. These may be abetted by immobility of much of the lung tissue, by inefficient cough mecha-

nisms, and possibly by bronchial deformities.

Functional difficulties can arise from all of these pathologic alterations: (1) The blood pumping action is inefficient and resistance is high in the atelectatic lung; (2) it is possible that peripheral resistance may be increased by loss of capillaries in the very long-standing traction emphysema; (3) infectious complications, particularly bronchiolitis, leading to ultimate restriction of the finer air passages may add a factor of tension emphysema with its mechanical consequences, as well as the effects of hypoxia in producing spasm of vessels; hypoxia is favored also by inefficient ventilation associated with the deformity of the chest; (4) implicit in the fibrosis resulting from the effects of the recurrent pneumonitis are loss of effective capillary bed and development of pulmonary-bronchial arterial anastomoses.

Effects of Mitral Stenosis

The segment, left atrium to pulmonary vein proximal to a stenotic mitral valve, can be distended with only a slight rise in pressure to accommodate a large volume of blood, until the elastic limit is reached (Sarnoff and Berglund, 1952). Beyond that point, the pressure-volume curve bends sharply, indicating that a slight increment in volume will result in a very large increase in pressure. *Exercise tends sharply to increase the pressure* (Hickam and Cargill, 1948). Naturally, pulmonary capillary pressure must exceed that within the pulmonary veins.

In contrast with the effects of a rapid rise in hydrostatic pressure within the pulmonary capillaries, which have been discussed in Part I of this chapter, a slow rise to 60 mm. Hg or more, which actually exceeds the oncotic pressure by a factor of 2, can be tolerated without evident accumulation of intra-alveolar fluid. Earlier attempts to estimate capillary pressure by "wedging" of a catheter have been supplemented by the direct approach to the atrium by transbronchial puncture (Allison and Linden, 1953, 1955; Allison, 1956). Perhaps this may be ascribed to increased tissue tension in the altered lungs, or perhaps, in some measure, to an accommodating

lymphatic drainage.

Lungs long subject to venous hypertension undergo a whole series of variegated changes. The walls of the alveoli become thickened as a result of a combination of factors: collection of edema fluid; deposition of hemosiderin and fibrosis; and infiltration of cells which are predominantly of the mononuclear type. Recurrent intrapulmonary hemorrhage is frequently observed, and the resulting hemosiderosis may be severe. The lesions have been well described (Lendrum *et al.*, 1950). The blood probably comes from intensely congested venules in the bronchi as described by Ferguson and associates (1944), but these are, in fact, largely branches of the pulmonary veins, although true bronchial veins that drain into the azygos system have also been described by Gilroy and co-workers (1952). Magarey (1951) has demonstrated in the rat

that the focal distribution is assumed even when blood is introduced experimentally by way of the trachea, and he has studied the process quantitatively. The persistence of the focal hemosiderosis as demonstrated in roentgenograms is remarkable. Hemosiderin becomes enclosed within large mononuclear cells that are situated largely in the lumina of the alveoli. Ultimately, the deposition of hemosiderin in the walls of the distal respiratory passages appears to stimulate proliferation of fibrous connective tissue.

It has long been known that smooth muscle tends to become notably increased in the walls of the distal air passages of the lungs in severe mitral stenosis. This, too, may be a reflection of increased tissue tension and will contribute to the ultimate rigidity of the lung.

Striking vascular changes occur frequently and were described in some detail by Parker and

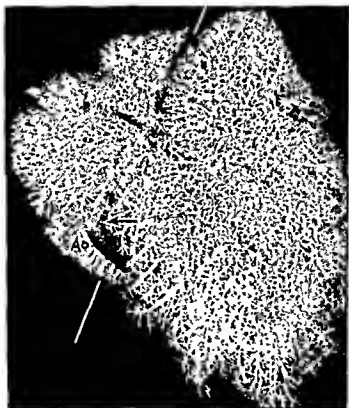


Figure XV-55. Cast of the lung derived from the kyphoscoliotic chest illustrated in Figure XV-54. The aorta (Ao) is bent upon itself, the sharp bend conforming to the apex of the kyphos as indicated by an arrow. The lower lobes (to the left of the white line) are remarkably atelectatic pyramidal structures. The upper lobe, however, is markedly overdistended, both in the anteroposterior and vertical axes.

Weiss (1936). The capillaries were described as reduced in number, and as having thicker walls than usual. Arteriolar lesions, especially intimal sclerosis and muscular thickening, have long been known and are similar to those in pulmonary hypertension produced by a variety of other mechanisms. Heath and Whitaker (1955) have indicated that their severity is in proportion to the degree of the arterial hypertension, but no such correlation with right ventricular hypertrophy has been found by Thomas and associates (1956) who suggest embolism as a better explanation. The interpretation of Evans and Short (1957) is that the thick media often observed is not representative of a "muscularized" arteriole, but of an arteriole in an abnormal state of contraction. Sclerosis of veins has been described (Brining, 1901).

Only recently have the necrotizing lesions been attributed to the hypertension *per se*, rather than to "rheumatic pneumonitis." There is, indeed, well-founded doubt that there is such a condition, if by this is implied some allergic pulmonary reaction analogous to the tissue response in the heart. Most lesions, called "rheumatic pneumonia" on the basis of clinical and roentgenographic signs, occur not during the phase of acute carditis, but rather in the stage of advanced heart failure in the long-standing extreme "tight" mitral stenosis. The so-called "Masson body" is certainly not pathognomonic of rheumatic disease. The condition, then, is probably better interpreted as a superimposition of pulmonary edema, and acute focal vasculitis often complicated by thrombosis and miliary infarction of the lung (so-called alveolar necrosis), upon the chronic lesion described above.

Since it has become possible to alleviate mitral stenosis surgically, the problem of "reversibility" of these vascular lesions has come very much to the forefront. Present evidence is conflicting. There is a suggestion that vascular spasm is an important factor here, too (Hickam and Cargill, 1948; Goodwin, 1956). This is understandable inasmuch as the pulmonary changes may result in anoxia. In other instances, however, apparently adequate surgical valvulotomy has not been attended with the expected relief of pulmonary hypertension, nor of right heart failure (Holling and

Venner, 1956). The residual effects of carditis upon the left ventricle, or of concomitant coronary disease may, of course, have some bearing on the ultimate result of the surgery.

In outline, the functional effects may be somewhat as follows:

1. Deficient oxygenation of blood with hypoxia from
 - a. Cardiac failure with pulmonary edema and hemorrhage and their products (intra-alveolar and interstitial)
 - b. Alveolar fibrosis (all of these factors result in "alveolo-capillary" block)
 - c. Increased pulmonary rigidity (Mack *et al.*, 1947)
2. Pulmonary hypertension from
 - a. Mitral stenosis itself
 - b. Residual effects of carditis as it involves the left ventricle
 - c. Loss of capillaries
 - d. Arteriolar changes of restrictive type
 - e. Hypoxia and possibly other factors associated with arteriolar spasm

EPILOGUE

A better understanding of cardio-pulmonary disease will be gained if the interplay of heart and lungs is viewed on the broadest stage; then, the details of narrower concepts, such as that of cor pulmonale, will be revealed in better perspective. At the same time, deficiencies in present understanding will become immediately apparent. These defects result, in part, from the difficulties in assimilating and correlating existing information from diverse disciplines. Moreover, many contradictory conclusions have been reached by various workers because of differences in concepts, techniques, or species under study, or because methods or observations have been inadequate or have not been accompanied by necessary controls. Among the particular needs are:

1. A better means of estimating the anatomic extent of the respiratory surface and vascular bed of the lung in its various components,
2. A thoroughgoing determination of the

mechanisms that are capable of inducing vasospasm in the lung; this implies further exploration of the autonomic nervous system,

3. A determination of the parameters of flow, pressure and time necessary to induce vascular changes in the lungs,
4. An investigation of the biophysical and biochemical mechanisms of these

changes, with particular reference to why they occur at lower pressures in the pulmonary arteries than in the systemic vessels, and

5. An accurate study of the anatomy of pulmonary emphysema and of the pathogenesis of the various forms.

When these are achieved, cardiopulmonary disease will be better understood.

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Clinicopathologic Correlations

GORDON B. MYERS

Pericardium	983	Myocardium	996
Inflammation	983	Congenital Anomalies	996
Acute and Subacute	983	Endocrine and Metabolic Lesions	996
Chronic, Constrictive	984-985	Degenerative Lesions	998
Endocardium	985	Chronic Anemia	998
Congenital Anomalies	985	Myocardial Dilatation and Hypertrophy, Hy-	
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Bacterial Endocarditis	995	Inflammatory Lesions	1012
Circulatory Lesions	996	Traumatic Lesions	1013
Neoplasms	996	Neoplasms	1013

Clinicopathologic Classification. In the evaluation of the cardiac patient, the first objective is the localization of the anatomic site of the lesion into one or more of the following major subdivisions, i.e., pericardium, endocardium, myocardium, great blood vessels. After anatomic localization, the second aim is the determination of the etiologic agent and its classification in one of the following broad categories of disease: (1) congenital, (2) endocrine or metabolic, (3) nutritional or toxic, (4) allergic, (5) degenerative, (6) circulatory, (7) inflammatory, (8) traumatic, (9) neoplastic, (10) functional. The third objective is the physiologic evaluation as

to (a) compensation, (b) presence or absence of manifestations of ischemia, and (c) rhythm. In this chapter, clinicopathologic correlations will be discussed according to the foregoing outline. The effort will be concentrated on the more common entities but will include some of the rare conditions. Owing to limitations of space, no attempt will be made to cover all entities, clinical conditions without accompanying pathologic manifestations, such as the arrhythmias, and pathologic conditions without accompanying clinical manifestations, such as some myocardial degenerations, will be omitted.

PERICARDIUM

Inflammation

The most important cause of pericardial disease is inflammation. Pericarditis is usually accompanied by the classical laboratory signs and the diagnosis is established, in the presence of an effusion, by examination of the aspirated fluid. Alternative etiologic agents that must be brought into mind, particularly in the presence of hemopericardium, include neoplasm (page 996), trauma, infarction

(page 1004), uremia (page 998), and those that cause non-inflammatory, nonbloody effusion, as in myxedema (page 987).

ACUTE AND SUBACUTE PERICARDITIS

Symptoms. Pain may result from irritation of the parietal pericardium of the anterior chest wall and diaphragm, or from contiguous pleurisy, but is absent in many cases, because the entire epicardium and much of the parietal pericardium are insensitive. Pericardial

pain is generally dull and oppressive, but may be sharp and stabbing. It may be distributed diffusely over the precordium, may be confined to the retrosternal area, or referred to the left side of the neck and shoulder by way of the phrenic nerve or to the abdomen by way of the lower intercostal nerves. Pain associated with pericarditis may simulate that of myocardial infarction or that of the acute surgical abdomen. Dyspnea varies with the size and rapidity of accumulation of the effusion and results chiefly from mechanical compression of the bronchial tree. Dry hacking cough is a frequent symptom, probably of reflex origin.

Chest Signs depend upon the character and amount of exudate. Fibrinous pericarditis is manifested by a superficial scratchy or leathery friction rub, usually audible in diastole as well as systole, but subject to variations in intensity and quality, occurring spontaneously or induced by modifications in pressure of the stethoscope. The friction rub may be evanescent or it may persist after development of effusion. Pericardial effusion may be distinguished from cardiac dilatation by the following physical signs: The apical impulse is either absent or faint and well within and above the percussion border in pericardial effusion, and is usually pronounced and adjacent to the left border of dullness in cardiac enlargement. The ratio of absolute to relative dullness is much greater in pericardial effusion, because of the tendency for the distended sac to displace the lung from contact with the ventral chest wall. Abnormal dullness in the second interspace to the left of the sternum is detectable in recumbent patients with pericardial effusion, because of distention of the cephalic portion of the sac, but is not found in uncomplicated cardiac enlargement. The cardiac sounds are more muffled and distant in pericardial effusion and may be accompanied by a pericardial friction rub. Pericardial effusion may be accompanied by distinctive compression signs, namely, tamponade, to be described below, and Ewart's sign, consisting of dullness and bronchial breathing at the angle of the left scapula, resulting from compression-

atelectasis of the left lower lobe. The roentgen shadow assumes the shape of a water bottle when the patient is erect, and is more globular when he is recumbent. Fluoroscopic reveals diminished to absent pulsations owing to the dampening effect of the fluid.

Cardiac tamponade results from elevation of intrapericardial pressure and consequent interference with diastolic filling. The chief clinical manifestations are: (1) elevation in systemic venous pressure, as evidenced by enlargement of the liver and abnormally dilated but nonpulsatile cervical veins; (2) shock with tachycardia and low pulse pressure secondary to reduced cardiac output; and (3) paradoxical pulse. Elevated intrapericardial pressure prevents the increase in venous return to the right heart, which normally compensates for the greater blood-containing capacity of the inflated lung. This uncompensated pooling causes left heart output and the pulse to fade during inspiration, to increase again on expiration as blood is forced from the deflating lung.

Electrocardiographic Signs are referable to underlying subepicardial myocarditis. The acute stage, or stage of injury, is characterized by elevation of the RS-T junctions with monophasic upright T waves in unipolar leads facing opposite ventricular surfaces and in the three standard leads. The QRS complex may be reduced in voltage, but is not altered in contour. As the lesion passes into the subacute phase, serial tracings reveal progressive return of the RS-T segments to the isoelectric line and increasing cove-plane inversion of the T waves in the same leads. With recovery, the electrocardiogram may return to normal.

Character of the pericardial fluid depends upon the etiology. Purulent effusions result from infections with pyogenic cocci; serofibrinous effusions are associated with rheumatic fever and tuberculosis; hemorrhagic effusions may occur in tuberculosis and in malignant neoplasms.

CHRONIC PERICARDITIS

Adhesive Pericarditis, resulting in obliteration of the pericardial cavity, and *adhesive mediastinopericarditis*, manifested by adhe-

sions to the thoracic cage and surrounding mediastinal structures, may be asymptomatic, provided there is no interference with diastolic cardiac filling or constriction of the great veins. Adhesions between the obliterated pericardial sac and the thoracic cage may be detectable clinically by the traction phenomena. In place of the normal systolic apical protrusion, there is systolic retraction of the soft tissues at the apex and perhaps systolic retraction of the ribs and interspaces between apex and sternum, followed by a sharp diastolic rebound. The apex remains fixed when the patient shifts into the left lateral or the right lateral position. Systolic retraction of the tenth to twelfth ribs in the left dorsal portion of the chest wall (Broadbent's sign) may result from diaphragmatic adhesions, but may also be associated with marked cardiac enlargement in the absence of pericardial disease. Despite these traction phenomena, cardiac function may remain normal as long as there is no interference with diastolic filling.

Constrictive Pericarditis limits diastolic ventricular relaxation and interferes with atrial and ventricular filling, thereby producing chronic cardiac tamponade. The chief complaint is generally referable to ascites with associated hepatic enlargement. Dyspnea is usually present on exertion. Peripheral

edema is late in appearance and relatively mild in degree. Although the clinical picture is suggestive of cirrhosis, the correct diagnosis is revealed by marked dilatation of the cervical veins. The elevation in venous pressure is more constant and more refractory to medication than that associated with myocardial failure and the dilated veins do not show the systolic pulsation usually present in congestive failure. Pulsus paradoxicus is almost invariable and the pulse pressure is low, owing to reduction in systolic pressure. A small quiet heart is the classical finding on physical and roentgen examination. Pericardial calcification may be demonstrable. The apical impulse, when detectable, is manifested by systolic retraction instead of the usual outward thrust and tends to be fixed in position with change in posture. Other traction phenomena, described above, may be present but are less common than in nonconstrictive mediastinopericarditis. In typical cases, the electrocardiogram reveals inverted T waves in all limb-leads and in most precordial leads, associated with QRS complexes low in voltage, but normal in contour. These changes are referable to involvement of the subepicardial portion of the myocardium. Atrial fibrillation is fairly common and is presumably the result of extension of the fibrosis into the atrial myocardium.

ENDOCARDIUM

From the anatomic standpoint, the lesions may be mural or valvular or both, or may involve more than one valve. The most frequent cause is inflammation but other etiologic entities include congenital malformations, circulatory lesions (valvular calcification, thrombotic endocarditis), trauma, and neoplasms.

Congenital Malformations of Heart and Great Vessels

Congenital malformations may be associated with anomalies in other parts of the body. Only a few of the cardiac anomalies of major importance will be discussed. The relation to maternal rubella early in pregnancy is noteworthy.

Patent Atrial Septum. Cyanosis is likely to be present at birth because of persistence of the right-to-left shunt from fetal life, but disappears promptly after establishment of postnatal pressure relationships in the two sides of the heart. Clubbing does not develop and cyanosis is absent during most of the life span because the pressure is greater in the left than in the right atrium and the blood consequently flows from left to right. Brief attacks of cyanosis may result from transitory reversal of shunt, precipitated by sudden rise of intrapulmonary pressure during coughing or straining; more prolonged cyanosis accompanies congestive failure. Stunting of growth is a consequence of large defects.

Dilatation and hypertrophy of the right

atrium and ventricle. The blood shunted from left to right atrium, added to that coming from the venae cavae, causes over-filling of the right atrium and ventricle, resulting in dilatation and hypertrophy of both chambers and augmented right-sided output. Right ventricular hypertrophy causes abnormal systolic lifting of the sternum and adjoining fourth and fifth costal cartilages on the left. When right ventricular hypertrophy develops early in life, it may give rise to a chest deformity characterized by protrusion of the lower sternum and adjacent left precordium. The right ventricular hypertrophy usually produces diagnostic signs in leads V_{3R} , V_1 and HV_1 characterized by either a late R wave preceded by a small Q wave or a late R' wave preceded by a small brief R wave, or by small brief R and S waves, a late intrinsicoid deflection with little or no S or S' wave, a depressed RS-T segment and a sharply inverted T wave. The right atrial hypertrophy may be manifested in the same leads by P waves 3 mm. or more in amplitude and 0.12 second or longer in duration, and is frequently complicated by atrial (auricular) fibrillation. Mural thrombosis is prone to occur in the dilated right atrium and constitutes a source for pulmonary embolism. Pulmonary infarction or pneumonia may precipitate right heart failure and thereby alter pressure relationships so that subsequent emboli pass through the septal defect into the systemic circuit.

Dilatation of the pulmonary trunk is a consistent finding produced by the increased right ventricular output and is recognized at the bedside by an abnormally forceful and extensive pulsation in the second and third interspaces to the left of the sternum. The pulsation is accompanied by a harsh systolic murmur and often by a systolic thrill and is followed by a diastolic shock and markedly accentuated pulmonary second sound. The dilatation may reach aneurysmal proportions and may be complicated by relative insufficiency of the pulmonary valve, manifested by a blowing diastolic murmur in the second and third interspaces along the left sternal border. Hoarseness may be produced by pressure on

the recurrent laryngeal nerve. The pulmonary conus is abnormally prominent in the roentgenogram and the dilated pulmonary arteries cause exaggerated comma-shaped hilar shadows that pulsate vigorously, producing the "hilar dance." The presence of a shunt from left to right atrium may be confirmed on cardiac catheterization by the demonstration of a significantly higher oxygen content in blood obtained from the right atrium than in blood obtained from the venae cavae. Anomalous entrance of a pulmonary vein into the right atrium and patent interatrial septum produce similar physiologic and clinical changes, but may be distinguished by angiocardigraphic visualization.

Mitral stenosis is a common associated lesion and is usually rheumatic in etiology, but is occasionally the result of a congenital defect. The obstruction at the mitral orifice raises the left atrial pressure and thus favors shunting of blood into the right atrium. The combination of mitral stenosis and atrial septal defect (Lutembacher's syndrome) produces greater right ventricular hypertrophy and greater dilatation of the pulmonary trunk than either lesion by itself and hence should be suspected in every case with exaggerated findings. The mitral stenosis is manifested by a rumbling diastolic murmur at the apex, best heard in the left lateral position, immediately after exercise, and is distinguished from uncomplicated mitral stenosis by the absence of the expected left atrial dilatation. The murmur simulating that of mitral stenosis may be audible in some cases of patent atrial septum in the absence of organic changes in the mitral valve; the murmur will disappear after surgical closure of the septal defect.

Patent Ventricular Septum is usually asymptomatic when it occurs as an isolated defect. Cyanosis and clubbing are absent, since blood is always shunted from the left to the right ventricle. The shunt is usually too small to affect cardiac size or function; a large defect may eventually produce right ventricular dilatation and hypertrophy and dilatation of the pulmonary trunk. The lesion is manifested by a long, harsh systolic murmur and usually by an associated thrill maximal in

the third and fourth interspaces at the left sternal border. The murmur is transmitted widely over the precordium and into the interscapular area, but not into the neck. The diagnosis may be verified by demonstration of a significantly higher oxygen content in blood obtained from the right ventricle than in blood from the right atrium. Occasionally there is an associated complete atrioventricular block, because of interruption of the bundle of His at the septal defect. Rarely, a high septal defect is accompanied by a fibrous band that distorts the aortic valve, producing insufficiency. Bacterial endocarditis is the commonest complication. Since the vegetations are prone to develop at the point where the cross-stream strikes the right ventricular wall, emboli are dislodged into the lesser circulation to produce pulmonary infarction.

Tetralogy of Fallot. Cyanosis and marked clubbing of fingers and toes constitute the most striking features. The cyanosis is caused primarily by shunting of unoxygenated blood from the right ventricle into an overriding aorta and into the left ventricle through a patent ventricular septum; it is intensified by a complicating polycythemia, secondary to chronic arterial oxygen-unsaturation. Cyanosis rapidly deepens during exercise, as a result of fall in arterial oxygen saturation and fall in oxygen consumption per liter of air ventilated through the lungs. Hyperpnea increases progressively during exertion, because of increasing tissue anoxia and rising level of blood lactate, and dyspnea and fatigue soon necessitate termination of exercise. The squatting or knee-chest position affords the greatest respiratory comfort, but orthopnea is absent. Stunting of growth is a common sequela of chronic anoxia. Dizziness, syncope, epileptiform convulsions, and focal cerebral manifestations may occur as a result of cerebral anoxia or thrombosis secondary to polycythemia.

The heart often appears normal in size on percussion and in the six-foot roentgenogram. Underlying right ventricular hypertrophy is usually manifested by abnormal systolic lifting of the sternum and of the adjoining fourth and fifth costal cartilages, occasionally by a

protruding deformity of this portion of the chest, and almost always by diagnostic patterns in leads V_{3R} and V_1 similar to those described under patent atrial septum.

The pulmonary trunk is usually small but may show post-stenotic dilatation. In childhood the hilar shadows are light and the lungs exceptionally radiolucent, but with advancing age the vascular shadows become more prominent as collateral circulation increases. The classical signs of pulmonary stenosis consist in a harsh systolic murmur with associated thrill in the second and third interspaces at the left sternal border, beginning with the first sound, attaining maximal intensity by midsystole and terminating before the end of systole, followed by a muffled, split-second sound; the thrill, however, is often absent, the murmur is frequently soft and occasionally absent, because of markedly reduced flow through a high-grade stenosis. A loud, but unreduplicated, second sound of aortic origin may be maximal in the pulmonary area when the aorta is displaced to the left. A right aortic arch is present in 25 per cent of the cases and is recognized by indentation of the right edge of the esophagus and by displacement of this structure towards the left.

Cardiac catheterization establishes the diagnosis of pulmonary stenosis by demonstrating an elevated pressure in the right ventricle but a significantly lower pressure in the pulmonary trunk. Arm-to-tongue circulation time is shortened, owing to the right-to-left shunt. Palliation is achievable by the Blalock operation.

Eisenmenger's Complex exhibits two of the features of tetralogy of Fallot, namely, dextroposition of the aorta and high ventricular septal defect, but is distinguished by the absence of pulmonary stenosis and the presence of a dilated or normal pulmonary trunk with increased pulmonary blood flow. Cyanosis develops in later childhood and gradually deepens; it cannot be fully accounted for by the degree of right-to-left shunt and is probably caused, in part, by progressive pulmonary vascular disease. The latter is accompanied by increasing pulmonary hyperten-

sion, which often gives rise to gross hemoptysis. Both right and left ventricular hypertrophy may be demonstrable clinically. A harsh systolic murmur and thrill are usually present at the base and may originate in either the dilated pulmonary trunk or dextroposed aorta, and the systolic murmur is often followed by a diastolic murmur along the left sternal border, resulting from pulmonary and, or, aortic regurgitation. The hilar shadows are prominent and may exhibit increased pulsations.

Subaortic Stenosis is manifested by signs that resemble those of rheumatic aortic stenosis but it is usually accompanied by an aortic second sound of good quality and not by aortic insufficiency and is more prone to be associated with post-stenotic dilatation of the aorta.

Isolated Pulmonary Stenosis is manifested by a valvular deformity developing during fetal life, after septal closure. The clinical findings are those of right ventricular hypertrophy, post-stenotic dilatation of the pulmonary trunk, a harsh systolic murmur with an associated thrill, maximal in the second and third interspaces at the left sternal border and extending throughout systole, a pulmonic second sound that is absent or widely split and, in contrast to tetralogy of Fallot, absence of cyanosis until the development of right heart failure. Pulmonary valvulotomy constitutes a direct repair of the deformity.

Endocardial Fibroelastosis. The essential feature is endocardial fibrosis, which limits diastolic dilatation of the heart in a manner analogous to constrictive pericarditis. The etiology is probably congenital, but in some cases it is thought to be inflammatory; in other cases, anoxic.

Patent Ductus Arteriosus is asymptomatic when the shunt is small. Exertional dyspnea, palpitation and eventual congestive failure result from large shunts. Stunting of growth may also occur when the shunt is massive. Hoarseness is a rare complaint, referable to pressure of the dilated pulmonary artery on the recurrent laryngeal nerve. Chronic cyanosis and clubbing are absent, because the blood flows from aorta to pulmonary trunk.

The diagnosis is based on the demonstra-

tion of a continuous harsh "machinery murmur," maximal in the second interspace to the left of the sternum, transmitted to the left clavicle and interscapular area, accompanied by a systolic or continuous thrill over the dilated pulmonary trunk. The murmur is accentuated late in systole and tends to envelop a loud pulmonic second sound. The continuity of the murmur from systole into diastole merely reflects uninterrupted blood flow from aorta into the pulmonary trunk. The diastolic portion of the murmur is absent in infancy because of lack of sufficient pressure-gradient between the aorta and pulmonary trunk, and may be absent in older children and adults if the shunt is small. Under these circumstances, exercise may increase blood flow and pressure-gradient sufficiently to convert a systolic into a continuous murmur.

The size of the heart depends upon the magnitude of the shunt. Since a large ductus may shunt 50 to 75 per cent of the blood expelled by the left ventricle, a twofold to fourfold increase in left ventricular output must be maintained for an adequate systemic circulation. This leads to left ventricular dilatation and hypertrophy. The excessive inflow into the pulmonary trunk causes dilatation, manifested by widening of area of percussion dullness and roentgen borders in the left second and third interspaces and by abnormally prominent pulsations in this area. When high pulmonary arterial pressures are maintained by a large shunt, right ventricular hypertrophy eventually develops. The oxygen content of blood obtained from the pulmonary trunk by catheterization is significantly higher than that obtained from the right ventricle, because of influx from the aorta. Excessive inflow into the pulmonary circuit ultimately increases pulmonary resistance and pulmonary vascular pressure to a point where it exceeds the aortic pressure, thereby reversing the shunt and causing cyanosis distal to the communication, i.e., in the lower, as compared with the upper extremities. With equalization of pulmonary and aortic pressures, the classical machinery-murmur disappears.

Peripheral signs, like those of aortic insuffi-

ciency, are present at rest, if the shunt is large. These signs may be absent at rest, but demonstrable after exercise, if the ductus is small. The high pulse pressure and water-hammer pulse are an expression of elevation of the systolic pressure associated with the increased left ventricular output, together with precipitous drop in diastolic pressure resulting from the escape of considerable blood from the systemic circuit.

Subacute bacterial endarteritis is the commonest complication. Since vegetations are prone to develop in the pulmonary trunk at the point of impingement of the stream from the ductus, emboli are released into the lesser circulation.

Coarctation of Aorta is often asymptomatic. When complaints develop, they are usually referable to either (1) intracranial hypertension (throbbing headache, dizziness) or (2) ischemia of lower extremities (numbness, coldness, intermittent claudication on walking, or delayed wound-healing). Left ventricular hypertrophy eventually becomes evident on physical, roentgen or electrocardiographic examination. Bicuspid aortic valve is a common associated anomaly. The proximal aorta is dilated, causing a pronounced pulsation at the episternal notch. A systolic murmur maximal in the left upper interscapular area is a common finding, probably arising from the turbulence in the vicinity of the coarctation. The presence of a stenotic lesion distal to the origin of the left subclavian artery is revealed by the following objective signs: The radial pulses are forceful, the strength of the right often exceeding that of the left; the femoral pulses are either impalpable or much weaker and somewhat later than the radials, owing to the circuitous course of the blood. The brachial systolic pressure is abnormally elevated; the femoral pressure is significantly lower and may be subnormal. Diastolic pressures are usually slightly to moderately elevated, but comparable in the four extremities, reflecting a uniform increase in peripheral resistance.

Collateral arterial circulation develops through anastomoses between the superior intercostal, scapular and internal mammary branches of the subclavian arteries and the

intercostal branches of the descending aorta and between the internal mammary and epigastric arteries. The dilated tortuous intercostal arteries are manifested by (1) visible or palpable pulsations, or by localized systolic murmurs; and (2) roentgenographic evidence of erosion of the lower margins of the ribs.

Complications. Rupture of the dilated aorta is an important cause of death. The long-standing hypertension may eventuate in cerebral hemorrhage or congestive failure. Subacute bacterial endocarditis may be engrafted on the commonly associated anomaly of bicuspid aortic valve or a comparable bacterial aortitis may occur at the site of coarctation.

Inflammatory Lesions

RHEUMATIC VALVULITIS

Active Rheumatic Valvulitis. During the course of acute rheumatic fever, changes in apical heart sounds may be produced by either acute *mitral valvulitis*, cardiac dilatation associated with myocarditis or extracardiac factors, such as anemia. Softening with prolongation or splitting of the first sound at the apex is a frequent early sign and may occur as a manifestation of prolongation in atrioventricular conduction or myocarditis, as well as early mitral valvulitis. The development of a blowing systolic murmur at the apex or of significant change in the quality of a pre-existent murmur is very common during acute rheumatic fever and may result not only from mitral valvulitis, but also from dilatation of the mitral ring in absence of a lesion of the leaflets. The differentiation during the acute phase of the disease is often difficult. A systolic murmur produced by acute inflammation of the mitral leaflet tends to replace the first heart sound and to extend through most of systole, whereas a murmur produced by dilatation of the mitral ring tends to follow the first sound and terminate earlier. The former is characteristically harsh or musical and well transmitted to the axilla; the latter is typically soft, blowing and poorly transmitted. Often the final decision must be postponed until long after subsidence of all signs of rheumatic activity. Murmurs resulting from organic mitral valvulitis should persist;

those caused by relative mitral insufficiency should disappear.

The development of acute *aortic calcutitis*, severe enough to cause regurgitation, is easily recognized by the appearance of a cavernous, blowing diastolic murmur in the third and fourth interspaces along the left sternal border. Murmurs referable to acute aortic or mitral valvulitis, which develop or undergo modifications during the course of acute rheumatic fever, may occur not only as a manifestation of acute rheumatic valvulitis, but also as a result of superimposed bacterial endocarditis. The latter is diagnosed in the presence of complicating systemic embolism and the etiologic agent is identified by blood culture.

Chronic (Inactive) Rheumatic Valvulitis is the end-result of healing of the acute inflammatory lesions by fibroblastic ingrowth and gradual formation of scar tissue.* Comparable deformities are prone to develop in the atrioventricular and aortic valves during the healing process. The regurgitation resulting from defective apposition of the acutely inflamed leaflets becomes permanently established as the healing causes retraction, and eventually becomes complicated by stenosis as the scar tissue causes thickening, stiffening and fusion of the leaflets. Thus, the healing of rheumatic valvulitis tends to produce ultimately a combination of insufficiency and stenosis; however, all gradations are observed both clinically and pathologically from a simple insufficiency to a relatively pure stenosis. The lesion is most common in and often limited to the mitral valve; aortic valvulitis is next most common; tricuspid valvulitis is much less frequent and is almost invariably accompanied by mitral stenosis. Lesions of the pulmonary valve are extremely rare. Clinicopathologic correlations will be made for each valve separately; multi-valvular lesions tend to produce summation-effects.

Chronic mitral calcutitis. Mild lesions may

merely cause mitral insufficiency; severe lesions usually produce combined insufficiency and stenosis, but less commonly may cause relatively pure insufficiency or stenosis.

Mitral insufficiency. Mitral insufficiency is manifested by a systolic murmur, loudest at the apex and transmitted towards the axilla. Organic mitral insufficiency caused by rheumatic valvulitis is distinguished from relative mitral insufficiency resulting from left ventricular enlargement by the quality and duration of the murmur and particularly by its effect on the first heart sound. The murmur of rheumatic mitral insufficiency is characteristically harsh or musical and tends to replace the first heart sound and to continue through systole, whereas that of relative insufficiency is typically soft and blowing, tends to follow the first sound and to fade in mid-systole. A systolic thrill is occasionally palpable at the apex in rheumatic mitral insufficiency. The degree of organic mitral regurgitation cannot be judged from the quality, intensity or duration of the murmur but can be estimated from the size of the left ventricle and atrium, provided other causes of enlargement of these chambers are excluded. On this basis, rheumatic mitral insufficiency may be divided into two grades, mild and severe. In the former, there is little reflux of blood into the left atrium, absence of cardiac enlargement, and an asymptomatic course, provided bacterial endocarditis does not develop. In the latter, there is considerable regurgitation of blood, leading to compensatory dilatation and hypertrophy of both the left ventricle and left atrium, secondary pulmonary congestion and right ventricular dilatation and hypertrophy. In practically all the cases with clinical evidence of marked organic insufficiency, some degree of stenosis is demonstrable at autopsy; in many of these, careful auscultation during life will disclose a short protodiastolic rumbling apical murmur which is representative of the stenosis.

Mitral stenosis. In a number of cases, the clinical signs are representative of a relatively pure mitral stenosis, consisting of a normal-sized left ventricle, a slapping rather than a heaving apical impulse, a snapping

* Inasmuch as the Aschoff body is the only acceptable pathologic criterion for rheumatic infection, old endocarditis which resembles that following rheumatic fever should be spoken of as "endocarditis of rheumatic type," unless the Aschoff body can be demonstrated (see pages 654 and 658).—Ed.

apical first sound demonstrably delayed phoocardiographically (interval between onset of Q and first sound averages .06 seconds as compared to normal of .04 seconds), little or no systolic murmur, a mitral opening snap, and a diastolic rumble which in slow hearts varies in duration with the degree of mitral stenosis. With milder degrees of stenosis, the murmur is usually confined to protodiastole, occasionally to presystole; with moderate degrees it is heard in both of these phases, but fades in mid-diastole; with severe degrees, it extends throughout diastole. The more pronounced murmurs are accompanied by a diastolic thrill. Mild mitral stenosis (Dexter's Stage 1, valvular area over 1.5 sq. cm.) may be manifested by physical signs of the lesion but no symptoms of cardiac insufficiency at sedentary activity. Moderate mitral stenosis (Dexter's Stage 2, valvular area between 1 and 1.5 sq. cm.) is likely to cause elevation of pressure in left atrium, pulmonary veins and capillaries at rest; and further increases in pressure during exercise are likely to precipitate pulmonary edema or hemoptysis. When the cause of the elevation in pressure is mechanical obstruction of the mitral valve at this stage (associated with a normal left ventricular size) rather than an undiscovered mitral insufficiency or myocardial failure (associated with an enlarged left ventricle), the most dramatic effects are achieved by mitral commissurotomy. Further progression to a severe mitral stenosis (Dexter's Stage 3, valve area less than 1 sq. cm.) leads to further rise in pulmonary capillary pressure followed by narrowing of the pulmonary arteriolar bed; at first this may be spastic, later sclerotic. The mounting pulmonary congestion increases dyspnea at rest but the arteriolar narrowing tends to protect against abrupt increments on attempted exercise and thus may reduce attacks of acute pulmonary edema and hemoptysis. However, more severe pulmonary congestion is manifested by chronic pathologic changes in the lungs. The increased resistance from the pulmonary arteriolar narrowing gives rise to pulmonary hypertension, and to dilatation of the pulmonary trunk which is manifested by the fol-

lowing signs in the second interspace at the left sternal border: an abnormally prominent systolic pulsation, a diastolic shock, a blowing systolic murmur and an abnormally accentuated pulmonic second sound. Severe and long-standing dilatation of the pulmonary trunk may be accompanied by relative pulmonary insufficiency, manifested by a cavernous blowing diastolic murmur following the second sound in the second and third interspaces at the left sternal border, louder in the recumbent than in the erect position. This is known as the Graham Steell murmur and resembles that of aortic insufficiency in quality, but differs in location and in postural influence; however, it can be diagnosed only in the presence of marked dilatation of the pulmonary trunk together with absence of peripheral signs of aortic insufficiency.

The gradually increasing pulmonary congestion is manifested by slowly increasing exertional dyspnea for a long but variable period of time. Compensation is maintained through right ventricular dilatation and hypertrophy, the signs of which have been described on pages 985 and 986.

Sudden failure may be precipitated by the advent of atrial fibrillation, pulmonary embolism, bronchopulmonary infection, or by acute myocarditis associated with recurrent rheumatic fever. Chronic right ventricular failure is prone to occur eventually and is usually gradual in development. The advent of chronic right ventricular failure marks the transition to Dexter's Stage 4. When the primary cause is mechanical obstruction of the mitral orifice, commissurotomy generally achieves worthwhile results in Dexter's Stage 3 but carries a high operative mortality rate in Stage 4.

Mitral insufficiency and stenosis are always demonstrable pathologically in long-standing cases of rheumatic mitral valvulitis and may be manifested clinically by a combination of signs described above under the appropriate headings. The association of considerable regurgitation with obstruction to the mitral orifice tends to produce greater enlargement of the left atrium than does pure mitral stenosis.

As the left atrium dilates, it extends back-

ward and to the right. The enlargement of the left atrium is detectable roentgenologically, both by direct visualization in the oblique position and by compression and displacement of the esophagus. The latter is occasionally sufficiently marked to produce dysphagia. In long-standing cases, the left atrium may reach enormous size and may form the right boundary of the heart.

Aortic valvulitis. At the advent of acute rheumatic aortic valvulitis, a cavernous blowing diastolic murmur, best heard in the third and fourth interspaces along the left sternal border, may constitute the only clinical sign. As healing occurs, this murmur persists and tends to lengthen in duration, to increase in intensity and to be transmitted to the left axilla. Although audible in the second interspace at the right sternal border, the diastolic murmur of rheumatic aortic insufficiency is loudest along the left sternal border. Sooner or later peripheral signs of aortic regurgitation appear and are proportionate to the degree of regurgitation. The earliest evidence is an increase in pulse pressure which results primarily from lowering of diastolic pressure, secondarily from elevation of systolic pressure. Water-hammer pulsations, characterized by sudden impact and precipitous collapse, become visible and palpable in the peripheral arteries. The elevation in systolic pressure is disproportionately great in the femoral, as contrasted with the brachial artery, and the abruptness of the systolic distention of the femoral artery gives rise to a pistol-shot sound over the vessel. Other peripheral signs that may be elicited, not only in aortic insufficiency but also in other conditions accompanied by high pulse pressure and peripheral arteriolar dilatation, include Duroziez's sign, a to-and-fro murmur heard upon application of pressure to a stethoscope over the femoral artery; and Quincke's capillary pulse, an alternate blanching and flushing of the nail bed, brought out during pressure against the tip of the nail.

A systolic aortic murmur, if not present during the acute stage, becomes audible in the second interspace at the right sternal border and is transmitted into the neck vessels.

As the valvular cusps thicken and stiffen, this murmur becomes louder, harsher, more prolonged and widely transmitted over the whole precordium. In the event of death at this stage, some degree of stenosis, as well as insufficiency, is generally demonstrable at autopsy; however, a clinical diagnosis of aortic stenosis is reserved for cases in which the murmur is accompanied by a palpable systolic thrill in the second interspace at the right sternal border, or by disappearance or marked diminution of the aortic second sound, or by typical peripheral signs, namely, a small-plateau pulse and low pulse pressure. In long-standing cases of rheumatic aortic valvulitis, stenosis may be the major or the only clinically demonstrable defect; however, some degree of associated incompetence is found at autopsy. During decompensation, the thrill of aortic stenosis disappears and the murmur tends to become muffled and softened; hence, the diagnosis may be missed if the patient is not re-examined after compensation is restored or if he dies during failure.

In chronic aortic valvulitis, a systolic and usually a diastolic murmur are audible at the apex. These murmurs are referable to an associated mitral valvulitis in the majority of cases, but may be produced at the mitral orifice in the absence of an intrinsic lesion. A systolic murmur, loudest at the apex and transmitted to the axilla, may be found as a result of relative mitral insufficiency secondary to left ventricular enlargement. A rumbling apical diastolic murmur and even an associated diastolic thrill, indistinguishable from that of mitral stenosis, may be found in isolated aortic insufficiency. This is known as the Austin Flint murmur and is prone to occur in association with incompetence of the posterior aortic cusp. Under these circumstances, the regurgitant stream is directed against the anterior leaflet of the mitral valve and tends to force it closed, thereby producing the diastolic murmur.

Both aortic insufficiency and stenosis tend to produce progressive left ventricular hypertrophy and dilatation, signs of which are described on pages 999, 1000 and 1001. Despite the chronically increased load on the

left ventricle, compensation is often maintained for years. Failure is often ushered in abruptly either by violent exercise or with a paroxysm of nocturnal dyspnea. Even though the patient survives the initial attack of acute left ventricular failure, the therapeutic response is generally poor and at first chronic left, then right ventricular failure supervenes.

Angina pectoris is present in a small percentage of cases of rheumatic aortic valvulitis, particularly when stenosis is the predominant lesion. The clinical coronary insufficiency may be correlated with independent coronary atherosclerosis in some cases, but occurs in the presence of relatively normal coronary arteries in others. In the latter, proper coronary filling may be hindered during systole by excessively high intraventricular pressure in aortic stenosis and may not occur during diastole in aortic insufficiency, as a result of the low diastolic pressure and regurgitation of blood, ordinarily available for coronary filling, into the left ventricle.

Syncope is not uncommon in aortic stenosis and is an expression of cerebral ischemia, usually because of inability of the left ventricle suddenly to augment its output, but is sometimes referable to a hyperactive carotid sinus reflex. Complete atrioventricular block and left bundle branch block may complicate rheumatic aortic valvulitis and may sometimes be correlated with extension of calcification from the base of the cusps into the membranous portion of the septum.

Tricuspid calcutitis is rarely an isolated lesion, but is almost invariably accompanied by mitral stenosis and insufficiency. The clinical manifestations referable to the mitral valvulitis appear first and those of tricuspid insufficiency become superimposed much later. Dyspnea decreases in severity, owing to shift of blood from pulmonary to systemic circulation, exceptions to this generalization being traceable to pleural effusion or massive ascites. On the other hand, cyanosis increases because of peripheral capillary stasis, and is frequently mixed with icterus, secondary to hepatic engorgement, to produce a green hue. Abdominal swelling from ascites is usually a prominent symptom and is generally dispro-

portionate to edema. In this respect, tricuspid regurgitation bears resemblance to constrictive pericarditis; the distinction is readily made in these cases by the venous pulsatile phenomena and right ventricular dilatation and hypertrophy characteristic of tricuspid regurgitation.

Elevation of venous pressure is evidenced by dilatation of the cervical veins in the erect position. The distinctive feature, however, is a systolic venous pulsation caused by regurgitation of blood through the tricuspid orifice into the venae cavae, rather than the usual systolic collapse from atrial filling. The systolic pulse is well seen in the external jugular vein and is made out in the internal jugular vein by lifting of the sternomastoid muscle.

The discharge of blood from the right ventricle into the hepatic vein produces systolic swelling of the markedly enlarged liver, manifested by systolic protrusion of the right costal margin and a systolic expansion and descent of the liver edge. The rapid escape of large amounts of blood from the right ventricle into the liver causes protrusion of the lower right portion of the chest and tends to produce apical systolic retraction because of sudden reduction in intrathoracic pressure. Added to these pulsatile phenomena is systolic protrusion of the sternum caused by the associated right ventricular hypertrophy and dilatation. Although the foregoing signs may be observed during failure, as a result of relative tricuspid insufficiency as well as tricuspid valvulitis, they tend to clear up rapidly with therapeutic response in the former situation, but persist in the latter.

Auscultatory phenomena are of little significance in the diagnosis of tricuspid disease inasmuch as murmurs derived from the associated mitral valvulitis are often audible in the tricuspid area and are similar in quality to tricuspid murmurs. Tricuspid regurgitation tends to produce a systolic murmur, loudest at the xiphosternal junction. The association of tricuspid stenosis with mitral stenosis is postulated when there are two rumbling diastolic murmurs, one localized at the tricuspid area, the other at the apex. Intensification of tricuspid murmurs characteristically occurs

during inspiration, owing to augmentation of right ventricular inflow during this phase of the respiratory cycle; on the other hand, mitral murmurs are louder during expiration. The combination of tricuspid stenosis and insufficiency may result in double pulsation in the cervical veins, the first impulse being caused by contraction of the hypertrophied right atrium, the second by systolic discharge of blood from the right ventricle into the superior vena cava.

SYPHILITIC AORTIC INSUFFICIENCY

The principal cardiac lesions caused by syphilis, namely, aortic insufficiency and narrowing of the coronary ostia, represent complications of the inflammation and scarring of the root of the aorta. Extension of the inflammation from the aorta into aortic cusps is responsible for rolling of the free margins of the latter. These processes, combined with dilatation of the root of the aorta from syphilis, tend to produce pure aortic incompetence.

Clinical Differentiation of Syphilitic from Rheumatic Aortic Insufficiency is based chiefly on (1) evidence of dilatation of the aorta in the former and a normal-sized aorta in the latter, and (2) signs of pure aortic regurgitation in the former, as contrasted with varying degrees of associated stenosis in the latter. The dilatation of the ascending aorta that constitutes a forerunner of syphilitic aortic insufficiency is first detectable roentgenologically and later is manifested by significant physical signs in the second interspace beyond the right sternal border, namely, an abnormal pulsation, percussion dullness, a soft blowing systolic murmur, and an accentuated tambour aortic second sound. Severe calcification of the ascending aorta is often demonstrable in the roentgenogram. Siform dilatation or saccular aneurysm of the arch or descending aorta may also be present and aids in establishing the syphilitic etiology of the lesion clinically.

Significant differences in the character and distribution of murmurs associated with syphilitic and rheumatic lesions of the aortic

valve can often be made out clinically and can be correlated with differences in the underlying lesion. The systolic component of the murmur in syphilitic aortic insufficiency is short and soft and represents vibration of the aortic walls, produced by eddy-currents set up in the dilated aorta; the systolic component in a healed rheumatic lesion is long and harsh and is eventually accompanied by a palpable thrill, representing coarse vibrations in the stiffened cusps projecting into the outflowing stream. On the other hand, the diastolic component of the murmur is generally longer and more intense in the syphilitic lesion, reflecting the greater degree of regurgitation. Furthermore, the diastolic murmur in syphilitic aortic insufficiency is well heard along the right sternal border and is often maximal in this area, as the result of the dilatation of the aorta to the right, whereas the corresponding murmur in rheumatic aortic insufficiency is poorly heard to the right of the sternum and is almost invariably maximal along the left sternal border.

Although mitral valvular lesions are not produced by syphilis but are generally present in patients with rheumatic aortic insufficiency, auscultatory findings at the apex are of little help in clinical differentiation, because of the fact that syphilitic aortic insufficiency produces left ventricular enlargement and relative mitral insufficiency and at the same time may be accompanied by a rumbling diastolic (Austin-Flint) murmur at the apex, simulating that of mitral stenosis. The Austin-Flint murmur is prone to occur when the posterior cusp is incompetent, permitting the regurgitant stream to strike and partially close the anterior mitral leaflet. The rumbling apical diastolic murmur thereby produced may simulate that of organic mitral stenosis in quality, may equal or exceed it in intensity and, indeed, may be accompanied by a diastolic thrill.

The peripheral signs of syphilitic aortic insufficiency are similar to those of rheumatic aortic insufficiency described on page 992, but are usually more pronounced, owing to the greater degree of regurgitation usually

associated with syphilitic than with rheumatic lesions and the absence of a stenotic component in the former.

Progressive left ventricular dilatation and hypertrophy are produced by syphilitic aortic insufficiency but compensation is often maintained for years after appearance of the valvular defect. Break in compensation is often sudden, taking the form of a severe paroxysm of nocturnal dyspnea or acute left ventricular failure during violent exertion. Even though compensation is restored, adequate exercise-tolerance is seldom regained. Left ventricular failure tends to recur soon and is likely to be followed by right ventricular failure.

Myocardial ischemia from narrowing of the coronary ostia is a contributory factor towards the failure in some cases. A clinical diagnosis of myocardial ischemia is permissible, however, only in the presence of angina pectoris or electrocardiographic signs of transitory subendocardial injury (page 1007). Under these circumstances, narrowing of the coronary ostia is generally demonstrable at autopsy.

BACTERIAL ENDOCARDITIS

The subacute form is superimposed upon valves damaged as a result of previous inflammation or congenital defects and is caused by growth of *Streptococcus viridans* or of other organisms of relatively low virulence. Entrance of the causative organism into the blood stream and growth on the damaged valve may often be traced to extraction of a tooth, tonsillectomy, or urethral instrumentation. The acute form may develop on previously normal valves and is caused by invasion of the blood stream by pyogenic organisms of high virulence, such as the *Pneumococcus*; however, correlation between clinical and pathologic findings follows similar patterns in the two forms of the disease. The main features are classifiable into three groups: (1) constitutional signs; (2) cardiac signs; and (3) embolic and vascular lesions.

Constitutional Signs. Fever is the commonest manifestation, but may be absent in terminal or very low-grade infections. It is

typically of the picket-fence type with chills and sweats but may be continuous or remittent. Leukocytosis is usual but not invariable. Progressive anemia develops and may be accompanied by tenderness over the sternum or other bones. Clubbing of the fingers is generally demonstrable in the subacute form of the disease. A positive blood culture is an expected finding if no antibiotics have been given. The existence of bacterial endocarditis is remote in the event of three successive negative blood cultures, provided the blood specimens have been taken after a chill or an abrupt rise in fever. Abnormal proteins, such as cryoglobulins, are frequently produced.

Cardiac Signs. When subacute bacterial endocarditis is engrafted on rheumatic valvulitis, it is not uncommon to find, in addition to the old rheumatic lesions, both clinical and pathologic evidence of recent reactivation of the rheumatic valvulitis. Changes in quality or intensity of pre-existent murmurs are prone to occur in subacute bacterial endocarditis but are not diagnostic, since they are also observed as a result of acute rheumatic valvulitis and extracardiac factors. Rupture of a valve, ulcerated by vegetations, produces particularly dramatic changes in the murmur. Acute bacterial endocarditis, during the course of a pyogenic infection, may be manifested by the abrupt appearance of a loud, rough murmur, generally systolic with mitral involvement and diastolic with aortic involvement. Acute bacterial endocarditis during the course of a pyogenic infection may be manifested by the abrupt appearance of a loud, rough murmur, generally systolic with mitral involvement, diastolic with aortic. Clinical and electrocardiographic evidence of complicating myocarditis (page 1012) is fairly common. The severe grades can be correlated with diffuse inflammatory lesions at autopsy. Myocardial infarction may result from coronary embolism.

Embolic and Vascular Manifestations. A wide variety of clinical and pathologic manifestations result from fragmentation of the vegetations and dispersal through the blood stream of emboli ranging in size from parti-

cles capable of obstructing major arteries to particles which lodge in arterioles or capillaries. The systemic circuit receives the emboli in most cases, since the vegetations are generally located on the mitral and, or, aortic valves; pulmonary embolism complicates vegetative endocarditis of the right side of the heart.

Large emboli, reaching the extremities, may produce typical clinical and pathologic signs of arterial occlusion. Much more frequent, and therefore of greater diagnostic value, are the clinical signs of arteriolar and capillary lesions in the skin and mucous membranes, presumably produced by minute emboli or by localized capillary inflammation. These consist of white-centered petechial hemorrhages, best made out in the conjunctiva, tender, blue-red nodules in the pads of the fingers and toes (Osler's nodes), and splinter hemorrhages in the nail beds.

Large emboli to the abdominal viscera give rise to sudden pain of a type and distribution characteristic of irritation of the peritoneal surface or capsule of the involved organ. Thus, a renal embolus of sufficient size to produce an infarct is manifested by sharp pain in the loin, which may radiate forward and downward to the groin, and is accompanied by hematuria. A more common renal manifestation is painless microscopic hematuria without renal insufficiency, which may be correlated with focal embolic glomerulitis. Acute diffuse glomerulonephritis with edema, hypertension and renal insufficiency, in addition

to the hematuria and albuminuria, is also encountered, particularly late in the disease, when the blood culture is sterile. The spleen is generally enlarged sufficiently to be detectable by palpation.

Cerebral embolism produces neurologic findings, which can be correlated accurately with the site of the lesion. Meningeal irritation with increased number of leukocytes or red cells in the spinal fluid is not uncommon, even in the absence of focal cerebral signs.

Circulatory Lesions

Circulatory lesions include calcification of the valves and thrombotic endocarditis. Calcific aortic stenosis is usually engrafted on subclinical rheumatic lesions of the aortic valve and is manifested by similar clinical signs. Thrombotic endocarditis is usually subclinical during life and is recognized at autopsy.

Neoplasms

Neoplasms may arise from or may lodge on the endocardium in some cases (discussed in section on Neoplasms) or may cause injury to the endocardium by a metabolic product, as exemplified by carcinoid tumor originating in the intestine or metastatic to the liver. This tumor may release serotonin in high enough concentration to produce tricuspid or pulmonary valvulitis, but the agent is destroyed in passage through the lungs so that the left side of the heart usually escapes damage.

MYOCARDIUM

The manifestations of myocardial disease may be either (1) associated with predominant findings referable to co-existing involvement of pericardium and, or, endocardium, or (2) referable to a predominant or exclusive myocardial lesion. The etiologic and clinical features of myocardial involvement associated with pericardial or endocardial disease have been discussed under the appropriate headings; the clinico-anatomic features, clinical and electrocardiographic manifestations and etiology of isolated or predominant myocardial involvement will now be discussed.

Congenital Anomalies

Idiopathic Hypertrophy includes glycolytic cardiomegaly. The signs are those of general cardiac dilatation or hypertrophy.

Endocrine and Metabolic Lesions

Acromegaly is accompanied by marked cardiac hypertrophy, predominantly left ventricular, which is caused in part by excess of growth hormone, in part by associated hypertension. Coronary sclerosis is a frequent complication.

Cushing's Syndrome and Pheochromocytoma may be accompanied by left ventricular hypertrophy because of hypertensia.

Addison's Disease. In untreated cases, the heart is small, the blood pressure low. During crisis, electrocardiographic signs of hyperkalemia may be present. Plasma potassium levels between 7 and 9 mEq. per liter are accompanied by church-steeple configuration of the T waves (increased amplitude, narrowing of base and sharpening of apex) and sometimes by a lengthening of the QRS interval owing to the appearance of a slurred S wave. Progressive rise in plasma potassium above 9 mEq./l. is marked by loss of P waves; and progressive broadening of the QRS, ending in a smooth biphasic QRS-T complex. Overtreatment with desoxycorticosterone leads to cardiac dilatation and failure with electrocardiographic signs of hypokalemia, namely, depression of the RS-T junctions with flattening or inversion of the T waves and lengthening of the Q-T interval.

Hyperthyroidism increases basal oxygen requirements by 25 to 100 per cent, thereby necessitating a corresponding increase in cardiac output. In patients with coexisting heart disease, the increased cardiac work imposed by hyperthyroidism causes increased hypertrophy and may precipitate failure. In most patients with uncomplicated hyperthyroidism, the heart is physiologically hyperactive, but anatomically normal; long-standing hyperthyroidism may, however, eventually lead to moderate cardiac hypertrophy, but very rarely causes failure, in the absence of other forms of heart disease.

The classical thyrotoxic cardiovascular symptoms and signs may occur in the presence of an anatomically normal heart and are referable to physiologic cardiac hyperactivity and to peripheral vasodilatation. Thus, the typical apical impulse is a diffuse, slapping, staccato movement caused by hyperactivity, and differs from the heaving impulse of left ventricular hypertrophy in its rapid rise and immediate fall and in the ease of obliteration by the palpating hand. Despite the diffuseness of the apical impulse, the heart is characteristically normal in size to

both physical and roentgen examination. A sharp, snapping apical first sound and a sinus tachycardia at rest are other typical features of physiologic hyperactivity. A systolic murmur is usually audible in the second and third interspaces at the left sternal border, because of dilatation of the pulmonary trunk, and a separate functional systolic murmur may be produced at the apex as a result of accelerated blood flow. Atrial fibrillation, paroxysmal or persistent, is a common complication of chronic hyperthyroidism in the older age group. Elevation in pulse pressure, owing to a rise in systolic in the presence of a normal or low diastolic pressure, is a common manifestation of increased cardiac output with peripheral vasodilatation and may be marked enough to give rise to a typical Corrigan pulse. Shortening of the circulation time is another classical feature. The electrocardiogram is not diagnostic.

Myxedema. The cardiac borders are widened to left and right on percussion and roentgen examination; the widening may result from cardiac enlargement from myxedematous infiltration and, or, from pericardial effusion. The apical impulse is usually imperceptible on physical examination and feeble on fluoroscopy. The heart sounds are faint and distant. The pulse is characteristically slow and small in volume, reflecting the reduction in cardiac output, consequent upon diminished oxygen consumption. Effusions of high protein content may occur into the subcutaneous tissue and into the pleural and peritoneal cavities, as well as into the pericardium, because of increased capillary permeability. The classical electrocardiographic signs consist in low voltage of P and QRS complexes and flattening or shallow inversion of the T waves, and may be largely caused by either the pericardial effusion or the myocardial lesion. Advanced sclerosis is a common complication of myxedema, but may be clinically asymptomatic until after the institution of treatment. Thyroid extract in proper doses causes (1) gradual return of the cardiac silhouette to normal (owing to absorption of pericardial effusion and, or, disappearance of cardiac dilatation); (2) concomitant improvement in

the force of cardiac contractions and pulse volume; (3) gradual absorption of subcutaneous and scrous effusion; and (4) increase in voltage of P and QRS complexes and change to upright T waves. Thyroid extract, particularly when given in large doses to myxedematous patients with coronary sclerosis, may precipitate angina pectoris or myocardial infarction, as the result of too abrupt an increase in demands upon the heart.

Beriberi. The underlying metabolic defect is a decrease in capacity to oxidize pyruvate and lactate, as a result of thiamin deficiency, the underlying physiologic change is peripheral arteriolar dilatation, perhaps secondary to accumulation of acid metabolites. Edema of the legs is often the initial symptom and may result in part from hypoproteinemia; dyspnea is often abrupt in onset and usually becomes severe in degree. Multiple neuropathy, if present, is mild, as severe incapacitating grades tend to protect against cardiac failure through limitation of activity. The effect of widespread arteriolar dilatation is like that of a large arteriovenous fistula in accelerating blood flow through the tissues, in augmenting return flow to the right ventricle, and in imposing demands upon the left ventricle for increased output, hence, the classical syndrome of right and left ventricular dilatation, high pulse pressure, Corrigan pulse, and shortened circulation time. The combination of dilatation of the atrioventricular orifices and great vessels with increased velocity of blood flow results in loud harsh systolic murmurs at apex and base and sometimes in a diastolic murmur along the sternal border, and the condition may be mistaken for organic aortic insufficiency. The diagnosis is established by the specific response to large doses of thiamine, characterized by restoration of compensation, disappearance of murmurs and peripheral signs, and return of cardiac size to normal.

Degenerative Lesions

Degenerative myocardial lesions may produce no physical signs until pathologic involvement is extensive when they may be manifested by the complex of circulatory col-

lapse from inadequacy of left ventricular output, by intractable congestive failure or, in the presence of diffuse myocardial fibrosis, by refractory failure similar to that associated with constrictive pericarditis and endocardial fibroelastosis. Prior to the advent of clinical manifestations, electrocardiographic abnormalities may be present. Certain etiologic types of myocardial degeneration may be suspected in the presence of cardiac manifestations or electrocardiographic abnormalities accompanying specific signs of the degenerative process in other organs, such as macroglossia and skeletal muscle enlargement in the presence of primary amyloidosis and neurologic signs in myotonia atrophica and Friedreich's ataxia.

Collagen Diseases may cause direct cardiac involvement through inflammatory lesions of coronary arteries (*e.g.*, polyarteritis nodosa), of the endocardium (Libman-Sacks syndrome), the pericardium (as in lupus erythematosus), or may indirectly involve the heart through the medium of systemic or pulmonary hypertension (systemic lupus erythematosus, polyarteritis nodosa). The clinical manifestations are those of the cardiac lesion, in addition to those of the underlying collagen disease.

Uremia. The myocardial involvement may be manifested by electrocardiographic abnormalities, the accompanying pericarditis by friction rub and occasionally by hemopericardium.

CIMONIC ANEMIA

Chronic anemia is compensated, in part, through increase in cardiac output and acceleration of circulation time. To accomplish the excessive work in the face of reduced arterial oxygen content, dilatation and subsequent hypertrophy of both ventricles occur. Dilatation of the great vessels and, or, the mitral and tricuspid rings, together with the accelerated blood flow, produces murmurs at one or more valvular orifices that may be mistaken for organic valvular disease. The commonest manifestation is a systolic blowing murmur in the second and third interspaces along the left sternal border (the so-

called hemic murmur), referable to dilatation of the conus and pulmonary trunk. When dilatation is great enough to cause insufficiency of the pulmonary valve, the systolic murmur may be accompanied by a cavernous blowing diastolic murmur in the same area. Comparable systolic and diastolic murmurs may rarely occur in uncomplicated anemia as a result of dilatation of the aortic ring, the systolic murmur attaining maximal intensity in the second interspace at the right sternal border, the diastolic in the third and fourth interspaces along the left sternal border. A systolic murmur that is loudest at the apex and transmitted to the axilla is a common finding in chronic anemia and is referable to dilatation of the mitral ring. Occasionally a rumbling diastolic murmur, resembling that of mitral stenosis, may occur in the presence of anemia without organic mitral valvulitis. Mitral and aortic diastolic murmurs are more prone to occur in sickle cell anemia than in other etiologic types and may lead to an erroneous clinical diagnosis of rheumatic heart disease.

The electrocardiogram in severe anemia may show depression of the RS-T segments and inversion of the T waves. These findings resemble those associated with myocardial ischemia from other causes and may disappear after correction of the anemia.

MYOCARDIAL DILATATION AND HYPERTROPHY SYSTEMIC HYPERTENSION

Systemic hypertension is the commonest cause of chronic left ventricular dilatation and hypertrophy. Other causes include certain valvular defects (aortic insufficiency, aortic stenosis, mitral insufficiency) and certain lesions requiring prolonged maintenance of high cardiac output (chronic hyperthyroidism, chronic anemia, and arteriovenous fistula, including not only the traumatic variety, but also those associated with osteitis deformans). As a sequel to localized myocardial injury or destruction, such as attends infarction or inflammation, compensatory hypertrophy of the uninjured myocardium develops even in the absence of hypertension, valvular defects or other factors that increase

left ventricular load. The signs applicable to primary vascular hypertension but also to the other causes enumerated above are discussed under the general heading of chronic left ventricular dilatation and hypertrophy, which essentially represents the cardiac response to a chronically increased left ventricular load.

Chronic Left Ventricular Dilatation and Hypertrophy. The commonest cause is systemic hypertension.

Physical signs. Left ventricular dilatation is recognizable at the bedside by displacement of the apical impulse outward beyond the left midclavicular line and downward into the sixth interspace or lower. Projection of the point of maximal intensity of the apical impulse more than 1 centimeter beyond the midclavicular line in the fifth interspace is most often caused by left ventricular dilatation, but may also be produced by right ventricular enlargement or mediastinal shift; the diagnosis is established by demonstration of associated left ventricular hypertrophy or by exclusion of the other causes in the course of the examination of the heart and lungs. Left ventricular hypertrophy is revealed clinically by a heaving apical impulse that lifts one or more ribs or causes a sustained and forceful protrusion of the soft tissues, which cannot be obliterated by the palpating hand. Left ventricular enlargement of sufficient degree to dilate the mitral ring is complicated by relative mitral insufficiency, manifested by a blowing apical systolic murmur that follows the first sound and is transmitted towards the axilla.

Roentgen signs. Concentric left ventricular hypertrophy causes increased convexity of the lower portion of the left cardiac border in P-A projection. As the left ventricle enlarges, its lower border projects downward into closer apposition to the diaphragm, its posterior border extends dorsally to fill the retrocardiac space, and finally its rounded lateral border bulges more and more towards the left.

Electrocardiographic signs. Left ventricular hypertrophy is manifested by QR complexes in leads V_5 , V_6 , V_7 and, or, V_8 , characterized by (1) a small Q wave measuring

0.02 second or less from onset to nadir and amounting to less than 25 per cent of the amplitude of the succeeding upstroke; (2) a prominent R wave consuming 0.04 second or more from onset to peak and exceeding 25 mm. in amplitude; (3) a late intrinsicoid deflection, beginning more than 0.05 second after the onset of the QRS; (4) a depressed, upwardly convex RS-T segment; and (5) an inverted (or, less typically, a flat to diphasic) T wave. The interval elapsing between onset and peak of the R wave and the amplitude of this deflection provide rough indices of the time required and voltage developed during passage of the impulse from endocardial to epicardial surface of the subjacent wall, the thicker the myocardium, the longer time consumed in inscription of the ascending limb of the R wave and the greater the voltage developed.

Symptoms of left ventricular failure. Dyspnea, the earliest symptom, is usually gradual in onset and progressive in development, appearing first during exercise formerly tolerated without discomfort, then during lesser and lesser exertion, and finally at rest. Dyspnea is caused chiefly by pulmonary congestion, which makes the lungs more rigid and resistant to expansion, thereby increasing the muscular effort of inspiration. The lessened elasticity of the congested lungs interferes with deflation and leads to an increase of intrapleural pressure, which adds to the difficulty of expansion. As failure increases, dyspnea is intensified by the need for maintaining increased minute respiratory volume to combat tissue anoxia, to reduce acidosis from accumulation of lactic and carbonic acids, and to increase dispersal of heat. Orthopnea, or labored breathing on recumbency, of sufficient severity to impel assumption of the erect position, is a cardinal symptom of left ventricular failure. The development of dyspnea on change from sitting to recumbent position is traceable to several factors: (1) increased pulmonary congestion consequent upon shift of blood from abdomen to lung and upon rise of pulmonary venous pressure owing to the necessity of lifting blood 4 to 7 centimeters to reach the left atrium; (2) elevation of the

diaphragm with reduction in vital capacity; and (3) cerebral venous engorgement. Paroxysmal nocturnal dyspnea is an acute attack of orthopnea, waking the patient after one to two hours of sleep. The background for the attack is chronic pulmonary congestion from left ventricular insufficiency; the events during sleep in the recumbent position that lead to the attack are progressive increase in pulmonary and bronchial congestion with complicating pulmonary edema, consequent upon transfer of blood and edema-fluid from the systemic circuit to the lungs; the precipitating factors that suddenly augment pulmonary engorgement and edema and awaken the patient in acute dyspnea include nightmares, muscular movements and paroxysms of cough. The shortness of breath persists for minutes to hours after assumption of the sitting position and is characteristically accompanied by cough, expectoration of a pink, frothy edema-fluid and wheezing, resulting from bronchial congestion with spasm and secretion of mucus.

Cough is not only associated with paroxysms of nocturnal dyspnea but also tends to be provoked by other activities or conditions that produce dyspnea, such as exertion and recumbency. The circumstances that bring on cough point to pulmonary congestion, rather than primary bronchial or pulmonary disease, as the cause. Gross hemoptysis may result from pulmonary infarction or from rupture of an engorged vessel.

Extracardiac signs of left ventricular failure. Pulmonary congestion and edema constitute the chief manifestations. The earliest evidence is obtained roentgenographically and consists in accentuation of hilar shadows and fanlike radiation towards the periphery at the bases; later, crackling râles are detectable at the bases and may be accompanied by sonorous and sibilant râles because of the presence of bronchial mucus and spasm. During acute pulmonary edema associated with a severe paroxysm of nocturnal dyspnea, moist and dry râles may be audible throughout both lungs. Hydrothorax may occur more often on the left side, in the presence of isolated left ventricular failure, but becomes predom-

inantly right-sided with coexistent right ventricular failure. Pulmonary emphysema develops after long-standing congestion, as a result of loss of elasticity.

Cardiac signs. Left ventricular enlargement is invariably present and tends to increase with the advent of failure. Protodiastolic gallop rhythm is often audible at the apex in left ventricular failure. The third sound is the result of increased intra-atrial pressure, causing a more forcible opening of the mitral valve and inrush of blood into a dilated left ventricle. Accentuation of the pulmonic second sound occurs as a result of pulmonary hypertension. Tachycardia is present even though the patient is at physical and mental rest. Pulsus alternans, characterized by regularly spaced beats that alternate in force as judged by systolic pressure and pulse volume, is an ominous sign.

Circulatory tests. Circulation time from arm to tongue is prolonged because of stasis in the lungs and systemic circuit. Arm-to-lung time and venous pressure are within normal limits in the absence of right ventricular failure. Vital capacity is reduced.

Acute Left Ventricular Dilatation may be precipitated in persons with previously normal hearts by an acute myocardial lesion of ischemic, inflammatory or toxic origin, particularly when accompanied by an abrupt increase in cardiac work consequent upon acute hypertension, a valvular rupture, or rapid intravenous administration of excessive saline or hypertonic solutions. The frequent discrepancies between the degree of dilatation and the extent and severity of the histologically demonstrable lesion may be explained by one or more of the following factors: glycogen content, electrolyte partition, and oxygen supply. The signs of left ventricular dilatation and complicating failure have been described above.

PULMONARY HYPERTENSION

Chronic Right Ventricular Dilatation and Hypertrophy are most commonly secondary to left ventricular failure, but may occur as the primary or major lesions as a result of the following conditions: (1) obstructive em-

physema, extensive pulmonary fibrosis, or rarely diffuse pulmonary arterial obstruction from sclerosis or thrombo-embolism; (2) valvular defects, such as marked mitral stenosis, pulmonary stenosis and insufficiency; and (3) increased return flow to the right ventricle, resulting from large interatrial or interventricular septal defects and acquired arteriovenous fistulae.

Physical signs. The apical impulse may be displaced to the left of the midclavicular line and may exhibit systolic retraction of the soft tissues, if there is relative left ventricular atrophy, as in marked mitral stenosis. Systolic protrusion of the lower part of the sternum and the adjacent fifth, fourth and perhaps the third costal cartilages in a normal adult chest (but not in a flat chest) is indicative of right ventricular hypertrophy. Increased percussion dullness in the left third and right fourth interspaces may be found in right ventricular enlargement, but not in isolated left ventricular dilatation. Dilatation of the conus pulmonalis is manifested not only by percussion dullness in the third left interspace, but also by abnormal systolic pulsation and diastolic shock in the third and second interspaces, together with a systolic murmur and an accentuated pulmonary second sound. Evidence of tricuspid regurgitation may accompany enlargement sufficient to involve the inflow tract.

Roentgen signs. Enlargement of the right ventricle first takes place in a ventral direction and may be detectable in the left oblique position when the ventrodorsal (anteroposterior) diameter is normal. The first evidence in the anteroposterior (A-P) view consists in increased prominence of the pulmonary trunk and conus, due in part to rotation and in part to dilatation. With marked enlargement, the cardiac shadow is widened, both to the right and left.

Electrocardiographic signs. Right ventricular hypertrophy may produce diagnostic signs in leads V_{3R} , V_1 , namely, either a prominent late R wave preceded by a small Q or a late R' wave preceded by small brief R or S waves; a late intrinsicoid deflection with little or no S or S' wave; and a sharply inverted T

wave. Typically, lead V_6 shows a small R wave, early intrinsicoid deflection and prominent S wave. This pattern is the reverse of that associated with left ventricular hypertrophy. Other patterns sometimes associated with, but not pathognomonic of, right ventricular hypertrophy include complete and incomplete right bundle branch block.

Clinical manifestations of right ventricular failure. Right ventricular enlargement is an almost invariable forerunner. Protodiastolic gallop in the fourth and fifth interspaces at the left sternal border may appear with failure, but is less common than the analogous protodiastolic apical gallop associated with left ventricular failure.

Elevation of venous pressure is an early sign and is recognized at the bedside by distention of the cervical veins when the patient is in the sitting position. When relative tricuspid insufficiency occurs as a result of dilatation of the inflow tract of the right ventricle, the dilated cervical veins may exhibit pulsation during ventricular systole in place of the usual collapse.

Dependent subcutaneous edema appears about the ankles and lower portion of the legs, if the patient is ambulatory, and gravitates to the sacral region and dorsal aspect of the thighs, if he is bedridden; it may extend over the entire lower half of the body into the chest wall, but does not involve the face as long as orthopnea is present, since the latter demands maintenance of the sitting position. The edema represents a primary renal retention of sodium and a secondary retention of water and chloride, resulting from decreased glomerular filtration and increased tubular reabsorption. Increased output of antidiuretic hormone may also contribute to the oliguria and water retention. The accumulation of fluid in dependent parts is the result of the influence of elevated venous pressure and the consequent increase in capillary hydrostatic pressure on formation of edema. Differences in tissue pressure also affect distribution of edema and account for massive accumulation in lax tissues and the paucity in nearby areas where the skin is more firmly attached to the underlying fascia. Other factors which may

contribute to cardiac edema include reduction in colloidal osmotic pressure from albuminuria, reduced protein intake and synthesis; increased capillary permeability secondary to anoxia; and impaired lymphatic drainage consequent upon elevation in venous pressure.

Engorgement of the liver is an early and often a persistent manifestation. During acute right heart failure there is progressive descent of the liver, accompanied by pain, tenderness and voluntary spasm in the right upper quadrant, during recovery there is gradual recession towards the costal margin. Chronic right heart failure is accompanied by a persistently enlarged, firm, nontender liver. The application of pressure to a passively congested liver causes increased dilatation of the cervical veins, because of the inability of the failing right heart to accommodate the increased return flow, whereas a similar maneuver in other forms of hepatomegaly has no effect on cervical venous pressure. Impairment of hepatic function is usually demonstrable in patients with congestive failure and is attributable to anoxia, secondary to reduced hepatic blood flow and stasis. Jaundice is an occasional finding in patients with uncomplicated congestive hepatomegaly, but is likely to appear after pulmonary infarction because of increased hepatic anoxia together with an excessive load of bilirubin. Anorexia and flatulence are common complaints referable to passive congestion of the gastrointestinal tract, and nausea and vomiting may accompany untreated congestive failure, as well as overdigitalization. Acute abdominal pain accompanied by blood in the stools and shock, clinically resembling mesenteric thrombosis, is a rare terminal event and may result from extreme engorgement of the gastrointestinal tract without demonstrable arterial or venous occlusion. Ascites may complicate passive congestion of the liver and gastrointestinal tract, but is less pronounced than subcutaneous edema, except when the right heart failure is caused by constrictive pericarditis or tricuspid insufficiency.

Dyspnea generally continues in lessened degree when right heart failure complicates

left failure and is no longer so likely to occur in nocturnal paroxysms because there is a reduction in pulmonary congestion, secondary to stasis in the systemic circuit. Shortness of breath, on the other hand, may persist or increase in some cases, as a result of accumulation of fluid in the pleural cavities. Hydrothorax is more common in combined left and right failure than in uncomplicated left failure, owing to interference with drainage through both the azygos and pulmonary veins, but does not accompany isolated right failure with normal pulmonary venous circulation. Hydrothorax associated with combined left and right failure is characteristically bilateral, but more marked on the right because of the greater tendency of patients to lie on their right side.

Cyanosis is an almost invariable manifestation and tends to increase when right-sided failure supervenes on left, because of peripheral stasis which permits increased deoxygenation of blood. Phlebotrombosis in the femoral vein or its tributaries is a common and important complication of peripheral stasis and may, in turn, lead to pulmonary embolism.

Circulatory test. Arm-to-lung time and arm-to-tongue time are prolonged. Venous pressure is elevated.

Acute Cor Pulmonale is produced by massive pulmonary embolism, rarely by massive pulmonary collapse, or by rupture of an aortic aneurysm into the pulmonary trunk. Death may occur within a few minutes from cerebral or myocardial anoxia or secondary ventricular fibrillation; it may occur hours later from right heart failure. In fatal cases of pulmonary embolism, there is only a rough correlation between the severity of the clinical picture, the length of survival, and the percentage of the pulmonary arterial tree found occluded at autopsy. Although embolic occlusion of more than 50 per cent of the pulmonary arterial bed is usually found in fatal cases, death may occur from smaller emboli, not only in debilitated, but also in robust persons, perhaps because of widespread reflex constriction of the coronary arteries and the nonembolized branches of the pulmonary ar-

teries. The clinical picture of massive pulmonary embolism is dramatic in onset and is usually characterized by sudden severe dyspnea, acute retrosternal oppression and, or, stabbing pleural pain, intense cyanosis, sudden weakness, dizziness, syncope or circulatory collapse. Shock may dominate the clinical picture and may obscure both dyspnea and chest pain. The objective signs may be classified into the following three groups:

Signs of pulmonary arterial obstruction. During the first few hours after a single large embolus, there is marked cyanosis, intense air hunger with rapid shallow breathing, but little or no abnormality to percussion, auscultation or roentgen examination of the lungs. Within 12 to 24 hours, cough, hemoptysis and pleural pain may appear and pulmonary infarction may be demonstrable as an area of consolidation, accompanied by fever and leukocytosis and resembling pneumonia. A hemorrhagic pleural effusion develops in some cases and jaundice may occur, especially if right heart failure is present.

Signs of right ventricular dilatation and failure. Rapid dilatation of the pulmonary trunk, conus and right ventricle may be demonstrable on physical or roentgen examination. The dilatation of the pulmonary trunk and conus is manifested by the following signs in the second and third interspaces at the left sternal border: a pronounced systolic pulsation, sometimes accompanied by a thrill; a loud, rough systolic murmur and sometimes a superficial grating sound, owing to impingement of the conus on the anterior chest wall; and a palpable and audibly accentuated pulmonic second sound. The physical signs of right ventricular dilatation and failure have been described above. Acute right ventricular dilatation and ischemia may be manifested electrocardiographically by (1) transient right bundle branch block, (2) displacement of the precordial transitional zone to the left, and (3) rapidly developing and receding cove inversion of the T waves in the first three or four precordial leads. These T wave patterns are distinguished from those associated with anteroseptal infarction by the fact that they are maximal in lead V₁ or V₂ and usually

confined to leads over the right ventricle, by their more rapid evolution and by the absence of abnormal QR deflections.

Signs of systemic circulatory collapse or shock result from drastic reduction in left ventricular output, consequent upon obstruction to blood flow through the lungs. The pulse is rapid and thready, the blood pressure low, and the skin an ashen gray or lavender hue. Syncope, coma or focal signs of cerebral anoxia may be present.

CORONARY SCLEROSIS AND OCCLUSION

Coronary Sclerosis and Thrombosis are pathologic rather than clinical entities, diagnosable during life by inference based upon clinical findings produced by myocardial infarction or ischemia. Thus, the symptoms, physical and electrocardiographic signs of the syndrome often designated clinically by the term "coronary thrombosis" may be correlated with myocardial infarction, but not directly with coronary thrombosis. This symptom complex accompanies myocardial infarction, irrespective of the presence or absence of underlying coronary occlusion. On the other hand, when localized coronary narrowing is sufficiently gradual in development to permit the establishment of an adequate collateral circulation, an occlusion may cause no demonstrable clinical manifestations or pathologic changes in the myocardium. Moreover, the symptom complex of angina pectoris and the accompanying electrocardiographic changes often ascribed to "coronary sclerosis" are referable to acute myocardial ischemia rather than to the alterations in the walls of the coronary vessels *per se*. Hence, correlations will be made between the clinical manifestations and the myocardial rather than the coronary lesion.

MYOCARDIAL INFARCTION

Acute Myocardial Infarction may occur without warning, particularly when associated with sudden thrombosis of a previously sclerotic but patent coronary artery, or may be preceded by significant premonitory symptoms, especially when there is rapidly progressive coronary narrowing sufficient to cause

myocardial ischemia, prior to actual infarction. Thus the sudden development of angina pectoris or an abrupt increase in frequency and duration of pre-existent angina may herald an impending infarction. The infarct may be precipitated by a sudden increase in the demands upon an ischemic myocardium imposed by exercise or excitement or it may occur during rest, as a result of further reduction in blood supply by thrombosis.

Clinical Manifestations

Pain is an expression of acute myocardial anoxia, as indicated clinically by its mode of onset and its constrictive, vise-like character, and confirmed pathologically by the invariable demonstration of anoxic lesions. The pain impulses are carried to the first to fourth thoracic segments by way of sympathetic afferents and are usually referred over the somatic connections of the same segments to account for the retrosternal location and radiation into the medial aspect of the arm, but may spread to cervical segments, resulting in a choking sensation in the neck, or to lower thoracic segments, resulting in epigastric or upper abdominal pain. In the latter event, the location of the pain, together with the commonly associated epigastric distention, nausea and vomiting, may lead to a false diagnosis of "acute surgical abdomen." The prolonged duration of the pain and the failure of vasodilating agents, such as nitroglycerine, are a reflection of the presence of severe and often irreversible anoxic degeneration; the pain eventually subsides spontaneously when the anoxic fibers undergo necrosis or recovery. The pain is submerged in some cases by overwhelming dyspnea or shock, or it may be absent if the nervous pathways are interrupted.

Sudden weakness and faintness are common complaints; a rapid pulse of small volume, lowering of systolic and pulse pressures, and cold clammy extremities are generally demonstrable as manifestations of reduced left ventricular output. Profound shock from marked fall in cardiac output may dominate the clinical picture; syncope or coma may result from transitory or prolonged cerebral ischemia.

Sudden dyspnea results from acute pulmo-

nary congestion associated with failure of the infarcted left ventricle and may constitute the major complaint or may be subordinate to pain or shock. In the former event, cough productive of copious pink, frothy sputum is often present and signs of diffuse pulmonary edema and bronchospasm are present (page 1000); in the latter event, crackling râles are demonstrable, at least at the lung bases. Acute pulmonary congestion throws a sudden load upon the right ventricle and may be followed by hepatic engorgement and elevation of systemic venous pressure. Acute pulmonary congestion is especially prone to precipitate right ventricular failure in patients with antecedent infarction or left ventricular failure.

Cardiac examination usually reveals enlargement (owing to antecedent left ventricular disease and, or, acute dilatation) and often discloses evidence of left ventricular failure (softening of the apical first sound in the presence of a normal second sound, protodiastolic gallop, accentuation of the pulmonic second sound). Pericardial friction rub is likely to be heard when there is an extensive fibrinous reaction, but is often not detectable when pericarditis is well localized. *Arrhythmias*: Premature systoles are prone to arise from injured muscle near the boundaries of the infarct and, when frequent or multifocal, constitute a forerunner of ventricular tachycardia and, or, fibrillation. Atrioventricular block may complicate acute posteroseptal infarction, but usually disappears during convalescence. Atrial fibrillation is a fairly common, usually transitory, complication and should lead one to search for evidence of atrial infarction, but may occur as a complication of infarction limited to the ventricles.

Fever, leukocytosis and elevation of sedimentation rate are manifestations of acute infarction and may be utilized as indices of the size of the infarct, provided other causes are excluded.

Complications and sequelae. Systemic embolism may occur as a result of detachment of a mural thrombus arising from the endocardial surface of a left ventricular infarct. Pulmonary embolism is a common complication,

generally originating from a phlebothrombosis in the lower extremities. Congestive failure, present during the acute stage, may prove therapeutically refractory or congestive failure may return or appear for the first time during convalescence. Rupture of the outer wall of the heart is a common cause of sudden death during the first three weeks. Rupture of the interventricular septum may be survived temporarily and is recognized by the appearance of a loud, rough systolic murmur and accompanying thrill, maximal in the fourth or fifth interspace near the left sternal border. *Ventricular aneurysm*: During the acute stage, the non-contractile infarcted myocardium tends to balloon out under the stress of the systolic intraventricular pressure; as the lesion heals by fibrous tissue replacement, the scar may continue to bulge, forming a permanent ventricular aneurysm. Systolic protrusion of an aneurysm of the anterior wall of the left ventricle may be manifested by an extensive impulse that lifts ribs or resists obliteration by the palpating hand. Fluoroscopic examination may reveal bulging and paradoxical systolic protrusion of a portion of the left ventricular wall. Shoulder-hand syndrome, consisting of (1) peri arthritis of the left shoulder, manifested by pain, stiffness, and limitation of joint motion; and (2) dystrophy of the left hand, manifested by pain, stiffness and swelling, may develop during convalescence, because of a combination of reflex muscular spasm, disuse and, in some cases, vasoconstriction of sympathetic origin.

Electrocardiographic Findings

Tracings taken with an exploring electrode applied to the thoracic cage or esophagus, paired with the Wilson central terminal as an indifferent electrode, represent chiefly the potential variations of the epicardial surface subtended by the exploring electrode. A sufficient number of such semidirect leads to cover the surface of the heart will provide enough evidence, not only for the establishment or exclusion of recent infarction, but also for a rough estimate of the distribution of the lesion between endocardium and epicardium and its size and location with reference to the cardiac

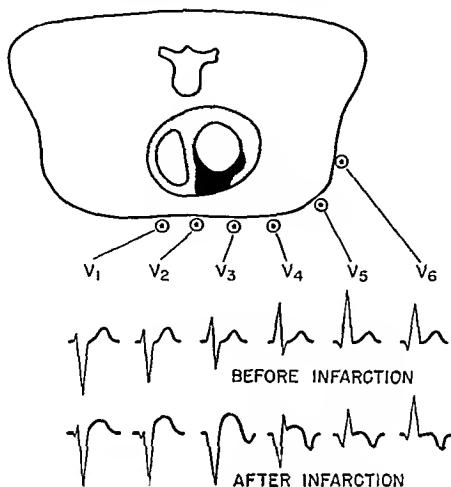


Figure XVI-1. Electrocardiographic findings in anterolateral apical infarction.

surface. Serial electrocardiograms will permit an estimate of the age of the infarct.

Electrocardiographic Estimation of the Distribution of an Infarct Between Endocardium and Epicardium is based chiefly on QRS configuration, but is sometimes aided by the RS-T pattern in leads from the left precordium, axilla, back, or from the lower esophagus, stomach or left leg. When the infarct is large, three concentric zones can be distinguished pathologically, and usually upon electrocardiographic examination as well: (1) a central zone of transmural infarction, extending through the entire wall from endocardium to epicardium; (2) a marginal zone of infarction confined to a portion of the wall, almost always the subendocardial layer; and (3) an outlying zone of ischemia, manifested by pallor and absence of histologic evidence of degeneration. If the infarct is small, only the

marginal and ischemic zones may be demonstrable.

1. *Findings in leads subtending a central zone of transmural infarction* (Figure XVI-1, lead V₃). The registration of an abnormal QS complex in a lead facing the epicardial surface of the left ventricle, which should normally exhibit an R wave as the major deflection, constitutes evidence of transmural infarction of the underlying wall. If the entire thickness of the subjacent myocardium is dead, the QS deflection has smooth descending and ascending limbs and the T wave resembles that in leads facing the left ventricular cavity (aV_R) and remains fixed in serial tracings. In the event of islands of acutely injured but living muscle in the more superficial layers of the transmural infarct, the QS deflection is notched or slurred, the RS-T complex is at first markedly elevated

and monophasic upright in contour and, in subsequent serial tracings, the RS-T junction gradually approaches the isoelectric line, and the T waves undergo progressive cove-plane inversion. If the central zone is small, semidirect leads may fail to show a QS deflection, but instead may show an abnormal QR complex referable to the surrounding marginal zone of subendocardial infarction.

2. *Findings in leads subtending a marginal zone of subendocardial infarction* (Figure XVI-1, leads V_4 ,). Abnormal QR patterns in left ventricular leads, characterized by an initial downstroke 0.03 second or longer from onset to nadir and more than 25 per cent of the amplitude of the succeeding R wave, are diagnostic of subendocardial infarction and are recorded at the margins of a transmural infarct, because of the tendency for such lesions to extend further on their endocardial than on their epicardial surface. A rough estimate of the relative thickness of the infarcted subendocardial and living subepicardial layers may be made from the time of onset to nadir of the Q, as compared with the time from onset to peak of R and from the relative amplitudes of the Q and R waves. The state of the living subepicardial layer is reflected in the RS-T segments and T waves. Acute injury to subepicardial muscle is manifested by elevation of the RS-T segment with monophasic upright T wave, subsidence of the injury to leave residual ischemia is accompanied by progressive return of the RS-T junction towards the isoelectric line, together with increasing cove-plane inversion of the T waves, decreasing ischemia and eventual recovery are marked by gradual decrease in the depth of the inverted T waves and eventual replacement by normal upright T waves. Preservation of the overlying subepicardial layer in acute subendocardial infarction permits registration of effects of acute subendocardial injury, namely, abnormal depression of the RS-T junction in overlying leads, with gradual return to the isoelectric line in serial tracings. In the rare cases where the marginal zone is characterized by infarction of the subepicardial layer and preservation of the subendocardial layer, the electrocardiographic findings

resemble those of acute pericarditis (page 984).

3. *Findings in leads subtending an outlying zone of ischemia* (Figure XVI-1, lead V_6) are characterized by a normal QRS pattern, an isoelectric RS-T junction and cove-plane inversion of the T wave, with gradual return to normal erect T wave, as recovery occurs. Leads over the uninvolved wall opposite an infarct (Figure XVI-3, lead V_4) tend to show patterns reciprocal to those recorded in leads facing the infarct, namely, exaggeration of the R wave, initial depression of the RS-T junction and progressive return to the isoelectric line, together with increasing height of the erect T waves.

Electrocardiographic Localization of the Infarct is based on the fact that tracings obtained through Wilson chest leads represent chiefly the potential variations of the epicardial surface subtended by the exploring electrode, and is made by mapping out the anatomic relationship of leads showing abnormal QS or QR patterns to the surface of the heart. Satisfactory correlation between the electrocardiographic estimate of the size and position of the infarct and the pathologic findings can be achieved, provided a sufficient number of semidirect leads is available to cover the surface of the heart and to delineate the zones of reference of the potential variations of the two ventricles. The customary positions for application of the exploring electrode are as follows: V_1 in the fourth interspace at the right sternal border; V_2 in the fourth interspace at the left sternal border; V_3 midway between V_2 and V_4 ; V_4 in the fifth interspace in the left midclavicular line; V_5 , V_6 , V_7 , V_8 , V_9 at the same horizontal level as V_4 , but in the vertical plane of the anterior axillary, mid-axillary, posterior axillary, scapular and paravertebral lines, respectively. Since positions V_4 , V_5 , V_6 , V_7 are at the level of the apex, exploration of the basal aspect of the left ventricle requires additional high leads taken at the intersections of a horizontal line at the level of the junction of the third interspace and sternum with vertical lines through the V_3 , V_4 , V_5 , V_6 , V_7 and V_8 positions. A prerequisite to the interpretation of multiple chest

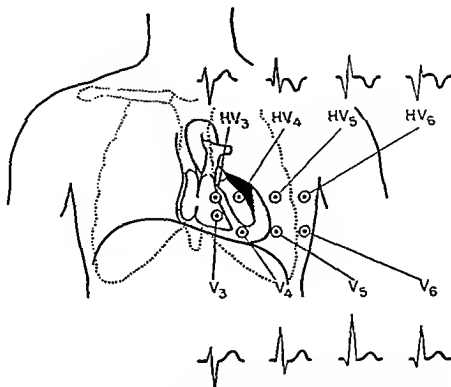


Figure XVI-2. Electrocardiographic findings in infarction of the base of the lateral wall of the left ventricle.

leads consists in the delineation of the transitional zone between the two ventricles in the lower and upper precordium and preferably in the back as well.

The transitional zone serves as an index of the projection of the ventral and dorsal ends of the septum onto the chest wall, and thus serves as a dividing line between the portion of the chest receiving predominantly the potential variations of the left ventricle and the portion receiving chiefly the potential variations of the right ventricle. When the transitional zone is in its usual position in the vicinity of lead V_3 anteriorly and near the mid-line posteriorly, the potential variations recorded through precordial leads at and to the left of the transitional zone (V_3 and V_4) come chiefly from the apical portion of the anterior wall of the left ventricle; those recorded through the usual axillary leads (V_5 , V_6 and V_7) come mainly from the antero-lateral, lateral and posterolateral aspects of the left apex, respectively; those recorded in back leads (V_8 and high V_8) and the low esophageal leads usually come chiefly from the posterior wall of the left ventricle; those in

leads from the left leg (aV_F), stomach and lower part of the back (below twelfth rib, but in the same vertical plane as $V_7, 8, 9$) come principally from the diaphragmatic surface. When the transitional zone is displaced to the left of the midclavicular line, as a result of dilatation of the right ventricle and, or, clockwise rotation of the heart, the potential variations of the anterior wall of the left ventricle are referred to the anterior axilla, those of the lateral wall to the posterior axilla. The following description of electrocardiographic abnormalities associated with the commoner sites of infarction is based on the assumption of normal cardiac position and would have to be modified, as described above, in the event of displacement of the transitional zone.

I. Infarction of the antero-apical aspect of the left ventricle. Small infarcts limited to the apical third of the anterior wall of the left ventricle are manifested by abnormal QR patterns localized to leads V_3 and, or, V_4 . Larger infarcts involving the apical half or more usually extend transmurally through a sufficiently large area to be manifested by abnormal QS patterns in lead V_3 and, or, V_4

(Figure XVI-1). Continuation into the basal aspect of the anterior wall is indicated by abnormal QR patterns in high precordial leads. Such lesions almost invariably extend subendocardially into the apical third or more of the lateral wall, producing abnormal QR patterns in leads V_5 and V_6 and generally continue around the tip of the left ventricle into the posterior aspect of the apex. Extensions limited to the apical third of the posterior wall are seldom recognizable in the usual chest and limb leads, extensions into the apical half or more of the posterior wall are generally manifested by abnormal QR patterns in lead aV_r , and in leads from the back below the diaphragm. Practically all large antero-apical infarcts continue into the adjacent interventricular septum and many produce QRS-T abnormalities in leads to the right of the septum (V_1 and V_2). A diagnostic pattern characterized by a QRS interval of 0.12 second or more, an abnormal Q wave and a prominent late R wave, an elevated RS-T segment or cove negative-T wave in right precordial leads may be correlated with transmural infarction of half or more of the septum. A diagnostic pattern, characterized by a QRS interval below 0.12 second, a small Q wave, a small R wave and deep S wave in right precordial leads may be correlated with transmural infarction of half or more of the septum. A diagnostic pattern characterized by a QRS interval below 0.12 second, a small Q wave, a small R wave and deep S wave in right precordial leads (V_1 and V_2 of Figure XVI-1), may be correlated with infarction of the left side of the septum. QS deflections accompanied by abnormal elevation of the RS-T segments in V_1 and V_2 may also be associated with septal infarction, but are not pathognomonic, unless accompanied by typical RS-T evolution in serial tracings. The occasional extension of large anterior infarcts across the septum into the adjacent anterior wall of the right ventricle does not produce localizing electrocardiographic signs.

2. *Infarction of the lateral wall of the left ventricle.* The commonest site in the lateral wall is the apical one-third, but most infarcts in this area are extensions of antero-apical

lesions, some are continuations of high lateral infarcts, a few represent extensions of posterior infarcts, and a few are primary in the apical portion of the lateral wall. Infarction confined to this area may be manifested by abnormal QR patterns in leads V_5 and, or, V_6 only, infarction extending into this area from other portions of the heart is manifested by abnormal QRS patterns in additional leads, depending upon the distribution of the remainder of the lesion. The most common primary infarct of the lateral wall is bullet-shaped with the base near the atrioventricular groove. Large infarcts of this type project sufficiently into the apical third of the lateral wall to produce abnormal QR patterns in V_5 , V_6 and, or, V_7 ; smaller infarcts, largely confined to the basal half of the lateral wall, are not detectable in these leads. Signs suggestive of high lateral infarction are often demonstrable in lead aV_L , taken with the exploring electrode on the left arm, but the diagnosis is established by abnormal QR or QS patterns in high axillary leads (high V_5 , V_6 and V_7), as exemplified by Figure XVI-2.

3. *Infarction of the posterior wall of the left*

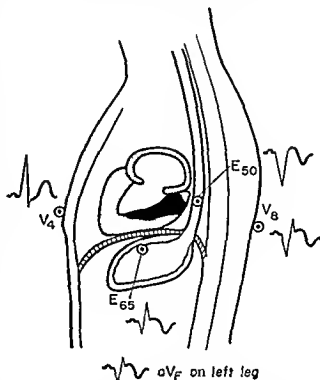


Figure XVI-3. Electrocardiographic findings in infarction of the posterior wall of the left ventricle.

ventricle is more likely to be missed electrocardiographically than infarction of the anterior or lateral walls, because the posterior wall is less accessible to exploration by surface leads, yet more subject to variations in anatomic relations, as a result of the influence of the height of the diaphragm. A portion of the posterior wall of one or both ventricles rests on the diaphragm; the remainder faces the posterior wall of the thorax. The major portion of the diaphragmatic surface of the heart is made up of the apical half of the posterior wall of the left ventricle when the diaphragm is low to normal in position and consists of right ventricle when the diaphragm is elevated. In the former situations (vertical to intermediate electrical position), the potential variations of the postero-apical aspect of the left ventricle have the predominant influence on leads from points below the diaphragm (left leg, lower back and stomach, Figure XVI-3), whereas the potential variations of the posterobasal aspect of the left ventricle are referred mainly to lower esophageal and back leads V_8 and high V_9 (Figure XVI-3), in the latter situation (horizontal electrical position), the potential variations of the right side of the septum and posterior wall of the right ventricle are transmitted downwards to be recorded in subdiaphragmatic leads, while those of the posterior wall of the left ventricle are transmitted to mid-back and high-back leads. The most common primary infarct of the posterior wall takes the form of a truncated cone with base paralleling the atrioventricular groove.

Smaller infarcts limited to the basal third of the posterior wall of the left ventricle may produce abnormal QR patterns in high V_7 , in lower esophageal leads and perhaps in V_8 , but not in low-back or left-leg leads. Larger infarcts extending through the middle third of the posterior wall will, in addition, be accompanied by abnormal QR patterns in lead aV_F and other subdiaphragmatic leads, provided that the heart is in vertical to intermediate position. On the other hand, if the heart is in horizontal position, large posterior infarcts may be undetectable in lead aV_F and in leads from stomach and lower back unless they extend sufficiently into the septum to produce

typical patterns of septal infarction (discussed above) in these leads. Complete atrioventricular block may accompany massive septal extensions of posterobasal infarction. Continuation of massive infarcts across the septum into the posterior wall of the right ventricle is fairly common, but does not significantly alter the electrocardiographic findings. Continuation of posterior infarcts into the basal portion of the lateral wall is manifested by abnormal QR patterns in high V_7 and high V_8 ; continuation into the apical portion of the lateral wall by diagnostic signs in customary V_7 and V_8 . Infarcts involving the apical, but not the basal, portion of the posterior wall usually represent extensions of anterior infarction, but are seldom recognizable electrocardiographically unless they involve more than the apical third of the posterior wall.

4. *Atrial infarction* may be manifested by rapidly changing ectopic atrial rhythms, serial changes in contour of the P wave, or in the position or contour of the PQ segment.

Electrocardiographic Estimation of the Age of the Infarct is based chiefly on a comparison of the RS-T pattern in serial tracings. Recent infarction is manifested by progressive changes in RS-T segment and T waves; healed infarction by a fixed pattern in serial tracings. In recent infarction with acute subepicardial injury, the RS-T junctions show abnormal elevation that changes from day to day, increasing if injury spreads, receding towards the isoelectric line as it subsides; the T waves are at first monophasic upright, then show increasing inversion of their terminal portions. With the disappearance of acute injury, the RS-T junction becomes stabilized, usually at the isoelectric level, and as organization proceeds, the T waves at first show increasing cove-plane inversion, then a much more gradual decrease in depth, and finally may return to a normal upright contour. Permanent fixed RS-T elevation and cove-plane inversion of the T waves associated with abnormal QS or QR patterns occur with healed infarcts that involve a sufficiently large area of the wall to form ventricular aneurysms. The QRS pattern is of less help in determining age and often remains constant in serial tracings,

even though the infarct is recent or organizing. However, significant changes in QRS pattern, found when adequate technical precautions are taken to insure against variations in electrode position, constitute evidence of activity. A definite increase in duration and amplitude of the Q wave at the expense of the R wave at a constant electrode position would indicate spread of an underlying subendocardial infarct towards the epicardium; change from normal QRS complexes at the boundaries of the lesion to abnormal QR deflections would indicate increase in area of infarction. On the other hand, abnormal QS and QR patterns found early in the stage of injury may show considerable increase in the R wave at the expense of the Q, if a portion of the injured myocardium recovers.

ANGINA PECTORIS

Angina Pectoris is a clinical syndrome, expressive of acute myocardial ischemia. Clinical and pathologic manifestations may be classified into two groups, namely, those referable to acute myocardial ischemia and those referable to the underlying disease.

Manifestations of acute myocardial ischemia. Anginal pain is an expression of acute myocardial anoxia, as evidenced by (1) its strangling character; (2) its precipitation by factors that suddenly increase demands on the heart (such as exertion), by factors that in addition may cause reflex coronary constriction (such as intense emotion, gastric distention or cold) or by factors that abruptly reduce oxygen content of arterial blood (such as inhalation of a mixture of 10 per cent oxygen and 90 per cent nitrogen); (3) the brief duration (usually less than 5 minutes), the prompt relief afforded by rest, by coronary dilators (such as nitroglycerine) or by inhalation of 100 per cent oxygen; and (4) the associated electrocardiographic changes.

Electrocardiograms taken during spontaneous or induced angina pectoris characteristically show acute RS-T depression of one millimeter or more, with a downward sagging or horizontal ST segment, usually accompanied by flattening or reversal in the T wave in leads overlying the ischemic area (V_3 - V_6)

with involvement of the anterolateral aspect of the left apex, V_7 - V_9 and aV_F with localization to the posterior wall, high axillary leads with ischemia high in the lateral wall. Repeat tracings after subsidence of the attack show prompt return to the pattern present before the onset of the attack. These electrocardiographic changes are referable to acute transitory injury to the subendocardial layer, as evidenced by the similarity to patterns produced in animals by mechanical, chemical or thermal injury confined to the subendocardial portion of the wall. Rarely, angina pectoris is accompanied by acute RS-T elevation in leads overlying the ischemic area, owing to subepicardial localization or transmural extension of the ischemia. QRS changes usually do not accompany brief attacks of angina pectoris unless the conduction system is involved, in which event transitory bundle branch block may be recorded.

Sudden death may occur as a result of ventricular fibrillation or cardiac standstill. If such a catastrophe should occur in a patient who had never had an attack of acute myocardial ischemia lasting more than fifteen minutes, pathologic examination might fail to show evidence of a myocardial lesion. In some cases, anginal pain and acute RS-T depression may last for one or more hours without clinical or electrocardiographic signs of gross infarction. This syndrome has been referred to as "coronary failure," in contradistinction to angina pectoris, on the one hand, and acute myocardial infarction, on the other. Should death occur during such an attack, pathologic examination reveals patchy myomalacia in the subendocardial layer, verifying the ischemic origin of the pain and the electrocardiographic localization of the ischemia in the subendocardial layer.

Manifestations of the underlying disease. The background for most cases of angina pectoris is marked narrowing or occlusion of one or more branches of the coronaries, owing to atherosclerosis; the underlying lesion in a minority is aortic valvular disease, either rheumatic or calcific aortic stenosis, or syphilitic aortic insufficiency with narrowing of the coronary ostia. Acute myocardial ischemia

rarely occurs in the absence of significant coronary narrowing or aortic valvular disease; in such instances the ischemia may be traced to severe anemia from sudden massive blood loss, to marked arterial aoxemia from pulmonary or congenital heart disease, or to a combination of marked hyperthyroidism and tachycardia. Hence, clinical establishment of angina pectoris constitutes presumptive but not pathognomonic evidence of coronary disease.

Inflammatory Lesions (Myocarditis)

There is often a lack of correlation between pathologic evidence of myocarditis encountered at autopsy and clinical and electrocardiographic manifestations found during life. The discrepancy arises in part from the fact that focal patches of acute myocarditis are demonstrable at autopsy in a number of patients in whom no cardiac lesion had been suspected during life. Some of these cases have escaped clinical detection, despite daily observation by a competent cardiologist and frequent serial electrocardiograms employing multiple precordial leads. The discrepancy is also explained in part by the fact that some patients with fatal infections have had physical or electrocardiographic changes attributed to acute myocarditis during life, but have shown no significant pathologic changes in the heart at autopsy. Nonspecific cardiac signs, which may develop during the course of severe infection, not only as the result of acute myocarditis, but also as a manifestation of extraneous factors, such as anemia, peripheral circulatory collapse, and hypopotassemia, include the following: tachycardia disproportionate to fever, softening of the first sound at the apex, even to the point of tic-tac rhythm; a blowing systolic murmur at the apex; or a mesodiastolic gallop rhythm, occurring at rates above 120. Nonspecific electrocardiographic abnormalities developing during the course of infection, which may be produced not only by myocarditis, but also by various metabolic abnormalities, particularly hypopotassemia, include RS-T depression, flattening or inversion of the T waves, lengthening of the Q-T interval, and prolongation of the P-R interval.

Correlation between clinical and pathologic findings is closer in patients with infections who develop myocarditis severe enough to threaten life. Demonstrable cardiac enlargement developing during the course of infection points strongly to acute myocarditis. The appearance of a protodiastolic gallop rhythm at rates below 100 in patients with severe acute infections also constitutes presumptive evidence of acute myocarditis. The development of congestive failure during the course of infection in a patient with a previously normal heart, who has not received excessive doses of saline parenterally, constitutes a basis for a diagnosis of acute myocarditis. Shock (characterized by ashen-gray cyanosis; rapid, thready pulse; and cold, clammy extremities) may occur during the course of acute infection, as a result of severe myocarditis, or as a result of peripheral circulatory collapse. In the former, the neck veins may be distended, whereas in the latter they are collapsed.

The following electrocardiographic abnormalities, developing during the course of an acute infection, can be correlated with acute myocarditis: complete A-V block; high-grade partial A-V block; low-grade A-V block not abolished by atropine; bundle branch block; and intraventricular conduction defects. Atrial fibrillation or flutter may occur as a manifestation of atrial myocarditis.

When the inflammatory process reaches the endocardium, mural thrombi may be formed in one or more chambers and may be dislodged to act as emboli in the systemic and, or, pulmonary circuit. The inflammatory process may also extend into the pericardium to give rise to typical signs of acute pericarditis (page 984). Idiopathic myocarditis is designated Fiedler's myocarditis and may be associated with endocarditis and sometimes with pericarditis.

Chronic infectious granulomas of tuberculosis and the mycoses, and sarcoidosis may occasionally develop in the myocardium but are usually undetected clinically unless numerous or large, or unless they undergo suppuration and break into the pericardium or through the endocardium.

The patchy acute myocarditis which occurs in some cases of trichinosis may be asymptomatic.

matic or may be accompanied by physical and electrocardiographic signs listed above as non-specific. Congestive failure is very rare. In echinococcosis, cysts are found in the heart in about one per cent of those infected. Calcified cysts have been demonstrated roentgenographically.

Traumatic Lesions

Penetrating Lesions. Hemopericardium constitutes the predominant feature in those surviving the first few minutes. Rapid accumulation of blood produces cardiac tamponade, manifested by a rising venous pressure, falling pulse pressure, feeble paradoxical pulse, and a quiet heart with muffled sounds and small excursions on fluoroscopy. The roentgen silhouette need not be grossly enlarged at the time the foregoing triad is present. The electrocardiogram may be negative when clinical manifestations of hemopericardium first become evident but sooner or later shows changes typical of pericarditis, namely, elevated, upwardly concave RS-T segments in leads from opposite surfaces of the heart, associated with a reduction in QRS voltage, but no abnormality in QRS contour. These RS-T patterns show the characteristic evolution of pericarditis, the junctions progressively approaching the isoelectric line and the T waves meanwhile undergoing progressive cove-planar inversion. When the injury has caused extensive myocardial contusion or when a coronary artery has been severed or ligated at operation, abnormal Q waves typical of those found in myocardial infarction are demonstrable. Valvular rupture in the course of the penetrating wound is manifested by a loud, coarse sea-gull type of murmur and is generally complicated by acute congestive failure. Septal perforation by injury is manifested by a continuous murmur, loudest in the vicinity of the septum and, if large, by prompt right ventricular failure.

Non-penetrating Injuries. Crushing injuries and direct blows to precordium from objects traveling at high velocity have caused cardiac rupture with hemopericardium, myocardial contusion, and rupture of a valve or chordae tendineae, even in the absence of fracture of the thoracic cage. Cardiac rupture from non-

penetrating injuries causes tamponade similar to that resulting from penetrating wounds. Gross myocardial contusion without rupture may be accompanied by symptoms, signs and electrocardiographic changes simulating those of acute myocardial infarction and may heal to leave a cardiac aneurysm. Death during the acute stage may result from ventricular fibrillation or standstill. Atrial injuries by indirect blows may be complicated by atrial fibrillation or flutter, generally transitory. Rupture of the aortic valve by non-penetrating injuries is manifested by the sudden appearance of a loud sea-gull diastolic murmur over the whole precordium, accompanied by peripheral signs of aortic regurgitation and by rapid development of congestive failure. Rupture of the mitral valve or chordae tendineae causes a loud, coarse systolic murmur and thrill, maximal at the apex and transmitted over the whole precordium, and is generally followed by congestive failure.

Extracardiac Injuries. Arteriovenous fistula developing after injury to contiguous walls of adjacent artery and vein (especially the femoral vessels) increases pressure and volume of venous return-flow to the right side of the heart and leads to right ventricular enlargement, elevated cardiac output and eventually failure.

Neoplasms

The majority of cardiac neoplasms found at autopsy produced no clinical manifestations during life. In some patients dying of malignancy with asymptomatic cardiac metastases, thorough cardiac examination has revealed nonspecific electrocardiographic abnormalities and occasionally diagnostic roentgen signs, namely, nodular irregularity in the cardiac silhouette.

Striking clinical features referable to the heart are present in a few cases of primary and metastatic neoplasm and are classifiable into the following syndromes:

Chronic cardiac tamponade may occur from neoplastic invasion of, or effusion into, the pericardium. A suspicion of neoplastic etiology is engendered by hemorrhagic character of the fluid and by rapid recurrence after tapping, and may be confirmed roentgenologically in

some cases by demonstration of nodules after instillation of air. A positive diagnosis has been established in some cases by demonstration of neoplastic cells in the aspirated pericardial fluid.

Superior vena caval obstruction without demonstrable bronchogenic or mediastinal neoplasm or aneurysm should suggest neoplasm of the right atrium.

Intractable congestive failure may be produced by extensive neoplastic invasion of the myocardium. An antemortem diagnosis may be possible through elimination of other causes of congestive failure and demonstration of irregularities of roentgen silhouette consistent with neoplasm. Clinical signs of mitral stenosis have been produced by myx-

oma of the left atrium and acute attacks of pulmonary edema have occurred from obstruction of the mitral orifice by a pedunculated tumor and have been relieved by changes in posture.

The development of atrioventricular block in persons with known malignant neoplasms may indicate metastasis to the nodal tissues, and the occurrence of unexplained atrial fibrillation should arouse the suspicion of atrial involvement by neoplasm.

A diagnosis of rhabdomyoma can be established clinically by the association of abnormalities in cardiac roentgen silhouette with mental retardation, tuberous sclerosis and adenoma sebaceum.

Surgery of the Heart

CHARLES P. BAILEY AND JOSEPH E. IMBRIGLIA

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Introduction

PATHOLOGY OF THE HEART is an old discipline while cardiac surgery is chiefly a development of the last few years. Nonetheless, in this short time, these two fields have influenced each other greatly. We shall discuss the important bearing which the pathologic aspects of cardiac lesions, both anatomic and physiologic, have upon surgical concepts and techniques, and also the converse effect, that of cardiac surgery and its diagnostic adjuncts in bringing about a more complete understanding of the pathology of the heart.

Pathologic Anatomy. The anatomic features of lesions of the heart which determine surgical concepts and techniques are: (1) type, (2) multiplicity, (3) size, and (4) position.

1. *Type of lesion.* Since the normal anatomy is the usual blueprint for surgical repair

of pathologic lesions, the greater the deviation of the pathologic anatomy of a lesion from the normal, the more difficult becomes its surgical correction.

2. *Multiple lesions,* in general, multiply the problems of the surgeon. Combined valvular lesions of stenosis and incompetence, particularly when affecting more than one valve, can pose great difficulties. Occasionally, one lesion may provide a certain degree of protection against the effects of another lesion, e.g., existence of a patent ductus arteriosus in association with the tetralogy of Fallot.

3. *Size of lesion* has considerable surgical significance. Dynamically those of minute size often may be ignored.

4. *The position of a lesion* determines to a considerable degree the surgical technique that may be used for its correction.

A lesion that is on or near the surface of the heart usually can be dealt with by accepted general surgical methods. On the other hand, lesions which are not easily reached from the surface frequently require special techniques, such as procedures carried out by a finger inserted into the "closed" heart or the use of hypothermia or cardiopulmonary bypass in "open" operations within the heart. The position of a lesion is important with respect to the specific chamber of the heart which must be encroached upon in the surgical repair. The risks and complications increase as we move from the atria to the ventricles and from the right side of the heart to the left.

Pathophysiologic Factors. The physiologic derangement resulting from lesions of the heart and great vessels may be profound and may have an important bearing upon surgical indications and techniques. Such derangements include impedance to blood flow, shunts, misdirection of course of blood flow, mechanical interference with myocardial action, and disturbances in conduction.

Impedance to blood flow may be caused by a simple mechanical obstruction, such as stenosis of a heart valve or coarctation of the aorta. Among other conditions which impede the effective forward flow of blood are regurgitation of a heart valve and presence of a ventricular aneurysm.

Effective surgical relief of an obstruction may bring about complete disappearance of the pressure gradient existing across the stenosis or at least may reduce it to physiologic insignificance. The secondary results of such an obstruction, however, such as pulmonary hypertension and the pulmonary arteriolar changes which may be seen in mitral stenosis or systemic hypertension in coarctation of the aorta, may improve but slowly after surgical relief of the primary lesion and sometimes may be completely irreversible.

Shunts. An intracardiac (atrial or ventricular) or an extracardiac (aortic) septal defect will permit free transeptal flow of blood from the higher into the lower area of pressure. Normally, pressures within the left cardiac chambers are higher than those within the corresponding ones on the right, and arterial pressures are higher in the systemic than in the pulmonary circuit. Hence, the direction

of transeptal shunting usually is from left to right.

Under three conditions a right-to-left shunt may become prominent. The septal defect may be so large that a considerable amount of mixing of the blood from the two circuits may take place. In this circumstance, a bi-phasic (both left-to-right and right-to-left) shunt will be present. In the vast majority of such cases the left-to-right shunt will be the larger or predominant one.

Should an obstruction of congenital type exist in the line of the circulation at a point distal to the septal communication, it will tend to direct the course of the shunting. Thus, congenital stenosis or atresia of the tricuspid valve will tend to cause a right-to-left shunt through an interatrial septal defect. A pulmonary stenosis of any type (arterial, valvular or infundibular) will tend to bring about a right-to-left shunt through either an atrial or a ventricular septal defect if one co-exists. On the other hand, coarctation of the aorta occurring beyond the site of an aortic septal communication will increase or augment the left-to-right shunting.

If a large left-to-right shunt has persisted for a considerable period of time, imposing additional work upon the right ventricle and causing engorgement of the pulmonary vascular bed, it may lead to secondary manifestations. The first observable effect of engorgement upon the pulmonary vascular bed is the development of increased arteriolar resistance. Subsequently the pulmonary arterioles show intimal hyperplasia, medial thickening and adventitial fibrosis. Ultimately, large numbers of arterioles become obliterated. The over-all pulmonary arterial resistance rises, becoming equal to and finally exceeding that in the systemic circuit. When this happens, the direction of the shunt from left to right becomes reversed.

Misdirection of blood flow. Anomalous pulmonary venous drainage, and transposition of the great arteries may cause misdirection of the course of blood flow. In the former condition, the physiologic abnormality resembles that associated with atrial septal defect, a left-to-right shunt being present. In the latter con-

dition, the underoxygenated systemic venous blood entering the right ventricle is propelled directly into the systemic arteries without passing through the lungs. On the other hand, the well-oxygenated pulmonary venous return is delivered by the left ventricle immediately into the pulmonary trunk.

Mechanical interference. Mechanical interference with myocardial contraction may result from such conditions as constrictive pericarditis, extensive scarring of the myocardium, and endocardial fibroelastosis.

Disturbances in conduction. While various types of atrioventricular "heart-block" are common in congenital heart disease, especially in septal defects, the organism usually has become so well adjusted to them that they do not serve as contraindications to surgery. However, sudden surgical interruption of the common conduction bundle often proves fatal.

Development of Principles. The first attempts to correct cardiovascular abnormalities followed the methods and techniques already established in general surgery. Drainage of pericardial effusions, suture of a stab wound of the heart, pericardiectomy for constrictive pericarditis, and grafting of well-vascularized adjacent tissues to the surface of the ischemic myocardium followed, in that order.

Surgery of the juxtacardiac blood vessels was initiated with the ligation of a patent ductus arteriosus (Graybiel *et al.*, 1938; Gross, 1939). Resection of a coarcted aortic segment (Crafoord and Nylin, 1945) was soon followed by anastomosis of the subclavian and pulmonary arteries (Blalock and Taussig, 1945). The method of replacement of resected arterial segments (Gross *et al.*, 1949) with fresh or preserved homografts subsequently was extended by the utilization of tubular plastic prostheses. The most elaborate of these techniques was Hufnagel's (1951) insertion of a plastic ball-valve into the descending thoracic aorta for the alleviation of aortic regurgitation.

The method of closed intracardiac surgery, at first accomplished by palpation with an instrument inserted through the wall of a vessel or cardiac chamber, was followed by insertion of a finger within the chambers of the beating heart to explore the lesion and to guide and control the instrument (Bailey 1948, published 1949).

Open heart surgery has progressed from the stage of simple occlusion of inflow (Varco, 1955, see Lillehei *et al.*, 1955) to occlusion of inflow with use of hypothermia to the body generally (Lewis and Taufic, 1953) and finally to total bypass of the heart and lungs (Gibbon, 1954). Later, it was found advantageous, especially in longer operative procedures, to utilize the patient's own lungs for oxygenation, merely bypassing the two sides of the heart (Dodrill, 1954, Blaneo *et al.*, 1956 and 1958). Induced cardiac arrest (Melrose *et al.*, 1955; Effler *et al.*, 1956; Lam *et al.*, 1956) may offer significant advantage in certain cases.

Atrial Septal Defects

Most defects of the atrial septum result from failure of proper fusion of the primitive septum primum with the septum secundum (defects of "ostium secundum"). In a smaller percentage the defects result from failure of union of the septum primum with the atrioventricular endocardial cushions (defects of the "ostium primum") or from failure in development of the endocardial cushions (common atrioventricular chamber). In uncomplicated cases a left-to-right shunt develops, overloading the pulmonary circuit; often this is associated with relative hypoplasia of the left ventricle and the aorta.

Three acceptable closed techniques exist for the closure of uncomplicated defects of the ostium secundum. In the more complicated defects an open technique is essential. Simple inflow (vena caval) obstruction with general bodily hypothermia (30° C.) will enable the surgeon to close many of these defects by direct suturing within the permissible limits of time (7 to 10 minutes).

If a longer operative period is desired, total cardiopulmonary bypass at normothermic temperatures is preferable. Should the defect be too large for direct repair by suturing, a prosthetic "patch" of formalinized polyvinyl sponge (Ivalon) may be used. It is our practice, in applying a patch, to use an "artificial foraminal valve" fabricated from Ivalon sponge. This prosthetic valve consists of a ring which is sutured to the margin of the defect

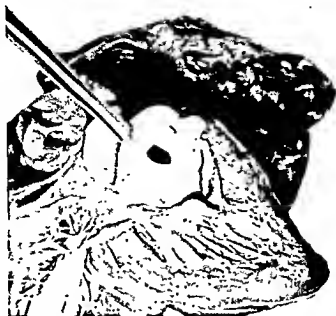


Figure XVII-1. Prosthetic "foraminal valve" used to close a large primitive atrial septal defect (endocardial cushion defect). The Ivalon-sponge flap will permit unidirectional continuation of the pre-existing shunt for several weeks after surgery.

and a structurally incorporated flap which opens into the appropriate atrium somewhat like the natural foraminal valve. Thus, a continuing but gradually diminishing one-way transseptal shunt is provided for a number of weeks during which time appropriate circulatory adjustments can take place gradually (Figure XVII-1).

Venous Communications

Under venous communications, we include various types of anomalous drainage: (1) of all the pulmonary veins, (2) of one or more of the left, or (3) of one or more of the right pulmonary veins into the right atrium or one of the systemic veins. All of these defects cause a left-to-right shunt and behave physiologically and clinically much like interatrial septal defects. However, reversal of the shunt obviously is impossible regardless of the presence or absence of pulmonary vascular changes.

In anomalous drainage of all the pulmonary veins, necessarily a large septal defect must coexist. Otherwise, no blood could enter the left side of the heart and life would fail. The more probable anatomic patterns are illustrated in Figures XVII-2A-C. Surgical correction may be carried out in one or two stages

and will vary with the anomaly and with the choice of a closed or open (total bypass) technique. In general, the surgical program must consist of primary establishment of free communication of the pulmonary venous confluence (or confluences) with the left atrium, followed by interruption of the communication with the systemic venous system. The co-existing atrial septal defect then should be closed, unless it can be utilized as a communicating passage between anomalous right pulmonary veins and the left atrium (see Figure XVII-3C).

Anomalous drainage of one or both of the left pulmonary veins may be treated by lateral anastomosis of the anomalous vessel (or vessels) to the base of the partially amputated left auricular appendage, followed by interruption of the systemic venous communication and closure of any coexisting atrial septal defect.

Anomalous drainage of one or both of the right pulmonary veins into the right atrium usually is associated with an atrial septal defect which characteristically lies in close proximity to the venous opening. If no conveniently located atrial septal defect is present, one may be created by incising the

interatrial septum. Then the anomalous stream may be diverted into the left atrium by way of the defect (Figure XVII-3A-C).

Should one of the right pulmonary veins drain into one of the venae cavae, it may be cut away from the cava and anastomosed to a contiguous normally or abnormally draining pulmonary vein. Should the latter situation exist, it then must be treated appropriately, probably as shown in Figure XVII-3C.

Ventricular Septal Defects

Communications between the ventricles are the result of failure of complete closure of the ventricular septum and usually involve the membranous portion.

Anatomic Closure. In patients over 3 years of age with a ventricular septal defect and a significant left-to-right shunt, in whom the systolic pulmonary arterial pressure is 50 per cent or less of that which exists within the aorta, the results of complete definitive anatomic correction are reported to be satisfactory (Lillehei *et al.*, 1958, Kirklin and McGoon, 1958).

Physiologic Correction. In patients with right ventricular pressures which vary from 50 to 100 per cent of those within the left ventricle, but with a left-to-right shunt, one cannot be certain whether one is dealing with a very large ventricular septal defect or with a significant degree of pulmonary vascular

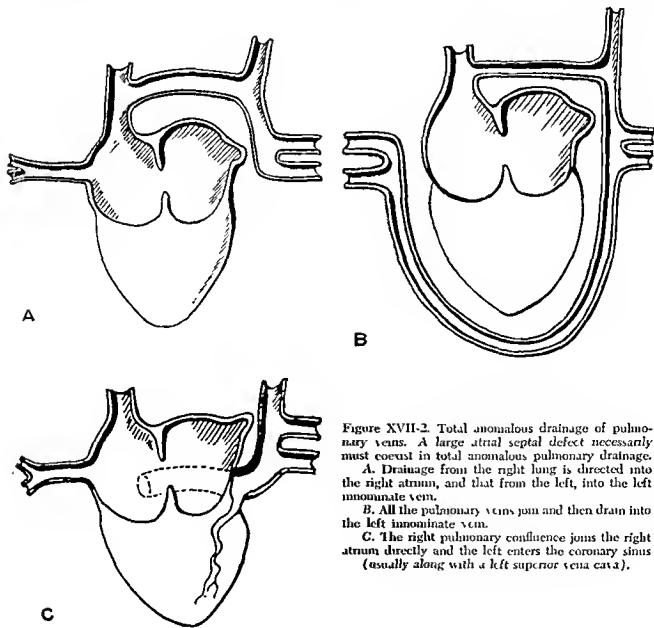


Figure XVII-2. Total anomalous drainage of pulmonary veins. A large atrial septal defect necessarily must coexist in total anomalous pulmonary drainage.

A. Drainage from the right lung is directed into the right atrium, and that from the left, into the left innominate vein.

B. All the pulmonary veins join and then drain into the left innominate vein.

C. The right pulmonary confluence joins the right atrium directly and the left enters the coronary sinus (usually along with a left superior vena cava).

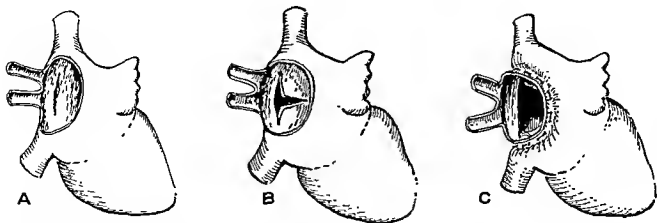


Figure XVII-3 Anomalous right pulmonary venous drainage into the right atrium in absence of an atrial septal defect.

A. A longitudinal incision is made through the posterior portion of the atrial septum, thus creating a septal defect in a convenient location.

B. The linear atrial septal defect is enlarged by making a ventral extension to the septal incision.

C. By suturing the lateral wall of the right atrium to the anterior edge of the newly-created defect, an enclosed passage is formed for complete diversion of the right pulmonary venous drainage into the left atrial chamber (From Gilman *et al.*, courtesy of *American Journal of Surgery*, 94:688, 1957.)

change, or both. Because the operative mortality in performing anatomic closure of such ventricular septal defects, especially in infants, has been high, the authors feel that many patients in this category should be submitted first to "physiologic" correction by creation of a controlled degree of pulmonic stenosis and, later, to anatomic closure of the defect. This method of surgical treatment of ventricular septal defect was first suggested by Edwards and associates (1948), performed by Bailey (1950, see Bailey, 1955, page 369) and popularized by Muller and Dammann (1952) (Figure XVII-4A, B). The surgical objective is conceived not to be anatomic closure of the defect, but elimination of the trans-septal shunt by equalization of the pulmonary and systemic arterial resistances. The amount of pulmonary arterial narrowing necessary varies from 60 to 90 per cent of the original arterial lumen and may be established in practice by adjusting the position of a partially occluding clamp until the systolic pressure in the distal portion of the vessel is reduced to 25-30 mm. of mercury.

Definitive closure of the septal defect may be undertaken in a patient "physiologically" operated upon after the lapse of a number of months or years during which time the lesion in the pulmonary arteriolar bed presumably

will have been demonstrated (by needle biopsy) to have regressed. At the time of the second operation, both the septal defect and the created "coarctation" of the pulmonary artery must be corrected.

In patients with severe pulmonary hypertension and a marked right-to-left shunt, surgical intervention may be contraindicated. In borderline cases the "physiologic" operation may be chosen or a prosthetic one-way "foraminal valve" may be sutured into the defect to permit its gradual closure with prolonged one-way valve "compensation" (Figure XVII-5A).

Patching the Defect. When the defect is large, techniques of direct suturing are inappropriate and a "patch" of compressed formalinized polyvinyl sponge (Ivalon) usually is applied. An error to be avoided is the use of a large, thin or flimsy patch which might swing into the outflow tract of the weaker ventricle and partially block it. It is safer, in all cases in which a patch-technique is necessary, to use a prosthetic "foraminal valve" that will permit gradual readjustment of the circulation by permitting continuation of a slowly closing one-way shunt (Figure XVII-5B) or, in nearly "balanced" cases, a slowly closing bidirectional shunt (Figure XVII-5C). It is our feeling, that except in

those individuals in whom the opening is but probe-sized, the pre-existing shunt should be preserved temporarily by such a valve.

Avoidance of Bundle of His. The upper and ventral margins of the "high" defect as seen from the right ventricle contain no conduction fibers. The risk of injury is concerned with the dorsal (right) and caudal margins of the defect (Truex and Bishop, 1958). Usually, the edge of the defect has a margin of white fibrous tissue, does not contain conduction fibers, and will hold sutures well. If the sutures are placed tangentially into this portion of the margin of the defect, total encirclement of the bundle may be obviated.

"Defects" of Aortic Septum

"Defects" of the aortic septum may take the form of complete or partial truncus arteriosus, aorticopulmonary arterial fistula, or patency of the ductus arteriosus. Of these clinical entities, only the last is encountered with clinical frequency. In these "defects," the characteristic direction of blood flow through the communication is from left to right. If prolonged and excessive, it will lead to pulmonary hypertension and arteriolar changes identical with those which develop with other large left-to-right shunts. In so-called "atypical" patent ductus arteriosus, the

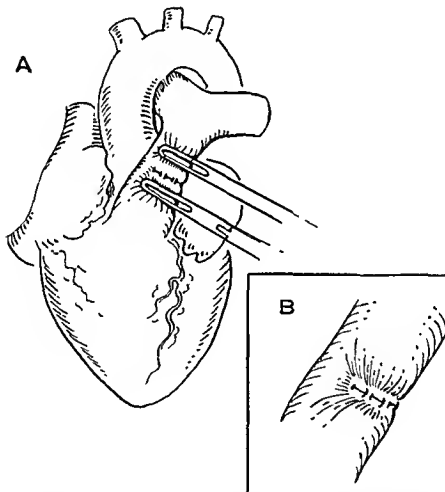


Figure XVII-4. "Physiologic" operation for relief of ventricular septal defect.

A. Clamps are applied partially across the lumen of the main pulmonary arterial trunk. After the distal systolic pressure is reduced to 20 to 30 mm. Hg, mattress sutures are applied to render this degree of narrowing permanent.

B. After removal of the clamps, the total pulmonary vascular resistance will have been raised to approximately the same level as the total aortic resistance, the transseptal shunt being abolished, or at least equalized (biphasic).

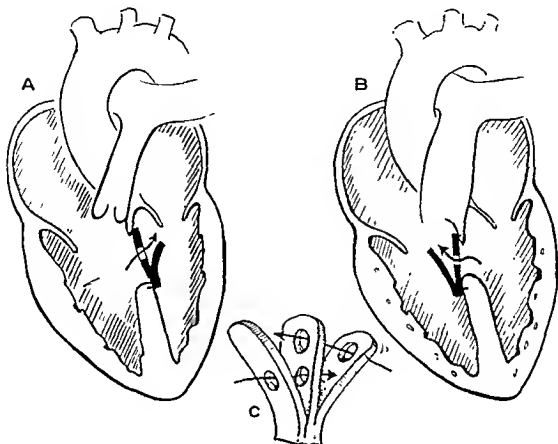


Figure XVII-5. Prosthetic foraminal valves.

A. One-way prosthetic foraminal valve applied in such a way as to permit transient persistence and gradual abolition of a pre-existing right-to-left shunt.

B. One-way prosthetic foraminal valve placed so as to permit temporary persistence of a left-to-right shunt (as in the usual ventricular septal defect).

C. Biphasic prosthetic foraminal valve which will permit gradual readjustment of the circulation and final closure of a septal defect in a case with "balanced" or biphasic shunt.

characteristic machinery-murmur is not present. If the shunt becomes "balanced," momentary variations in the respective opposing intra-arterial resistances and tensions may lead to shunting first in one direction, then in the other.

If the pulmonary arterial pressures exceed those within the aorta, an actual right-to-left shunt will take place through the communication.

Truncus Arteriosus. Since the advent of "open heart" techniques, many cases of truncus arteriosus have become amenable to surgical correction. Unfortunately the pulmonary artery or arteries may be too small for anatomic reconstruction in a normal pattern. Lesser grades of partial persistent truncus arteriosus may be corrected by longitudinal division of the artery and repair of the walls

of the newly created vessels. Great care must be taken that each of the coronary ostia thereafter will arise from the root of the newly created aorta rather than from the pulmonary trunk. Such an operation is best carried out by an open technique. However, a closed procedure has been successful in separating the two arterial circuits (Bailey, 1953; see Angulo *et al.*, 1953).

Aorticopulmonary Fistulae are readily correctible by an open technique. Alternatively, two appropriate suture lines may be placed prior to division, using a closed technique such as that described by Scott and Sabiston (1953).

Patent Ductus Arteriosus. Despite differences of opinion as to the relative merits of multiple ligation versus actual division and oversewing of the ductal ends, the over-all

rate of complete alleviation of clinical manifestation following surgery exceeds 96 per cent. If a "balanced" or "reversed" shunt exists, a prosthetic foraminal valve may be applied over the aortic opening of the ductus to permit gradual adjustment of the circulation. This requires an open operative technique.

Pulmonic Stenosis

Obstruction to the outflow from the right ventricle may be caused by congenital narrowing of the infundibular portion of this chamber (infundibular obstruction), by congenital fusion of the cusps of the pulmonary valve (pulmonary valvular stenosis), or by hypoplasia or atresia of the pulmonary trunk itself (Figure XVII-6A-C).

Diagnosis. The diagnosis of pulmonic stenosis is made readily by cardiac catheterization (right side) which reveals a characteristic pressure differential between the right ventricle, the infundibular chamber (if pres-

ent), and the pulmonary trunk (Figure XVII-7A-C). When an atrial septal communication exists in association with severe pulmonic stenosis, the pressure within the right atrium becomes elevated, especially during exertion. A portion of the right atrial (venous) blood then may pass through the defective septum, producing undersaturation of the blood in the systemic arteries.

Closed Method of Treatment. The definitive closed procedure for the relief of isolated pulmonic stenosis was established by the initial reports of Sellors (1948) and Brock (1948). The fused valve "cap" is divided instrumentally, forming a "bicuspid" valve, or the hypertrophied supraventricular crest is excised in part.

Open Method of Treatment. The work of Swan and associates (1953) and Dnrdill (1954) has established the unquestionable superiority of the open technique in valvular stenosis by which the rudimentary commissures may be opened to the fullest extent com-

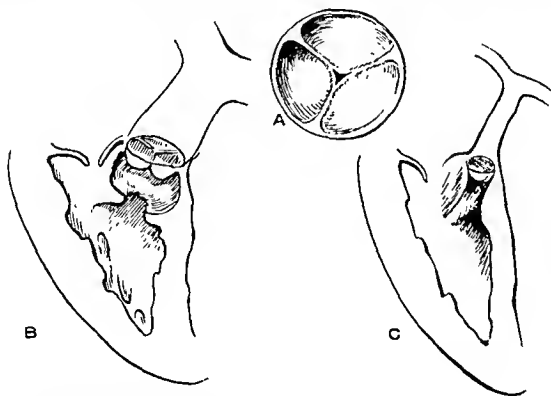


Figure XVII-6. Pulmonary stenosis.

A. Congenital fusion of the valve cusps.

B. Infundibular obstruction resulting from incomplete involution of the supraventricular crest.

C. General hypoplasia of the right ventricular outflow tract and pulmonary trunk. Note bicuspid valve, frequently encountered in such cases.

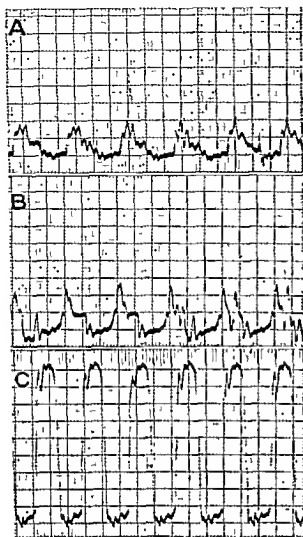


Figure XVII-7. Tracing obtained in catheterization of right side of heart in a patient with combined infundibular and valvular pulmonary stenosis.

A. Pulmonary arterial tracing.

B. Pressure curve obtained from the infundibular area.

C. Tracing of right ventricular pressure.

patible with competence. In valvular stenosis, hypothermia with temporary occlusion of the venae cavae has proved to be satisfactory for visualization of the valve and appropriate mobilization. In infundibular stenosis, cardiopulmonary bypass is preferable both because of the extreme irritability of the hypothermic ventricle and the extensiveness of the technical procedure which may be necessary.

Tetralogy of Fallot

Fallot (1888) described this condition as one which comprises (1) pulmonic stenosis, (2) a "high" defect of the interventricular

septum, (3) overriding of the first portion of the aorta, and (4) hypertrophy of the right ventricle. It now is felt that only the first two elements of the malformation are basic, the third frequently being an illusion, and the fourth being a consequence of the engendered overload of the right ventricle. In well-marked cases, the patient's cyanosis is deep and becomes more severe upon any physical exertion. The patient's capacity for activity is reduced markedly, and he tends to stoop or "squat" during recovery from any physical stress.

It is apparent that patients with this condition present a clinicopathologic spectrum which varies, on one hand, from that of a ventricular septal defect with insignificant pulmonary arterial narrowing and pronounced left-to-right shunt, to that of frank pulmonary atresia in association with a ventricular septal defect and consequent right-to-left diversion of the entire right ventricular content, on the other. Near the midpoint of this spectrum is the patient with moderate pulmonary stenosis and a ventricular septal defect with a nearly "balanced" shunt (Figure XVII-8A-C).

Blalock-Taussig Operation. Blalock and Taussig reported in 1945 the creation of an artificial patent ductus arteriosus by end-to-side anastomosis of one of the subclavian arteries with the right or left pulmonary artery. Thus operation permits a portion of the mixed arterial and venous blood which has entered the aorta to be recirculated through the pulmonary vascular bed for complete oxygenation (Figure XVII-9). In certain instances, even now, this is the operation of choice, as in extreme hypoplasia or atresia of the right ventricular outflow tract.

Potts-Smith Operation is a modification of the Blalock-Taussig procedure, a lateral anastomosis being created between the descending thoracic aortic and the left pulmonary artery.

Brock Procedure. Partial infundibulotomy or pulmonary valvulotomy, by removing a portion of the pulmonic obstruction, permits a greater portion of blood from the right ventricle to enter the pulmonary arterial tree for normal oxygenation and, ideally, should serve to "balance" the shunt. Theoretically, this

condition is identical with that of the patient who has undergone a "physiologic" operation for an isolated ventricular septal defect (Compare Figure XVII-8B with Figure XVII-4A, B). The extent of the operation may be controlled by measurement of the distal pulmonary arterial pressure, being terminated when the latter becomes elevated to a systolic level of 20 to 30 mm. mercury.

Open Correction of Both Defects. Definitive closure of the ventricular septal defect and simultaneous correction of the pulmonic stenosis with the aid of cardiopulmonary bypass offer a seemingly ideal approach to the treatment of the tetralogy of Fallot. Unfortunately, the operative mortality, especially in

small infants, has been extremely high, partly owing to impairment of the respiratory mechanism by the usual operative transection of the sternum and the double pleural intervention. Bleeding from the dilated bronchial circulation may be massive, causing incomplete visualization of the operative field which increases the risk of injury to the conduction system. A hypoplastic state of development of the pulmonary vascular bed may exist which will not permit the sudden establishment of a normal blood flow. In deeply cyanotic persons, therefore, it is unwise to perform a completely corrective operation without first making an attempt to prepare the pulmonary vascular bed to accept a normal

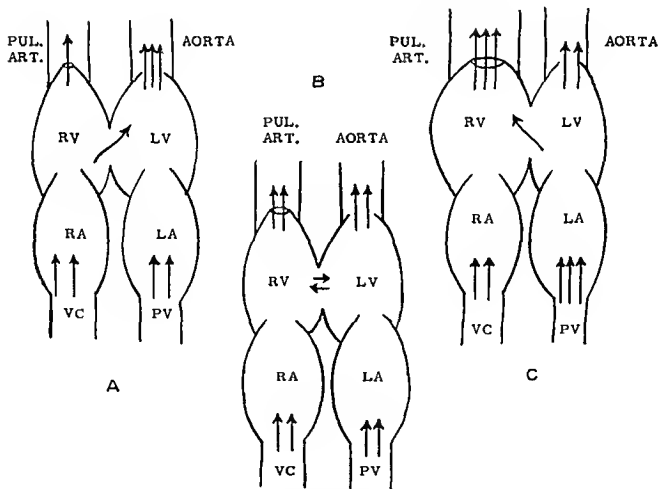


Figure XVII-8. Physiologic spectrum in ventricular septal defect associated with pulmonic stenosis (tetralogy of Fallot).

A. In severe pulmonary stenosis a right-to-left shunt occurs through the septal defect, bypassing the lungs and causing undersaturation of the arterial blood (cyanotic tetralogy of Fallot).

B. Moderate pulmonary stenosis with essentially no shunting (or a biphasic one) through the septal defect (acyanotic tetralogy of Fallot).

C. Slight pulmonary stenosis with shunt from left to right. The physiologic changes are similar to those seen in patients with isolated ventricular septal defects.

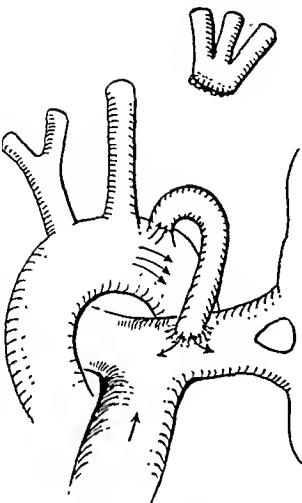


Figure XVII-9 Surgical creation of an artificial patent ductus arteriosus to alleviate the arterial oxygen desaturation characteristic of tetralogy of Fallot, subclavian-pulmonary arterial anastomosis (Bla- lock-Taussig operation).

time of blood flow. A systemic-pulmonary arterial anastomosis or a controlled Brock procedure of operative procedure would seem well designed to accomplish such preparation in small infants. In older children complete correction may be undertaken, using artificial "foraminal" valve type of prosthesis for closure of the ventricular septal defect; this permits a gradually diminishing left-to-right, right-to-left shunt to persist until the pulmonary vascular bed has become "dilated" sufficiently to accommodate the entire left ventricular output (see Figure XVII-1).

Constrictive Pericarditis

Organization of a pericardial exudate, most often that of tuberculous pericarditis, may

lead to restriction of cardiac diastolic dilatation by the constricting effect of the resulting leathery encasement of the heart. The output with each cardiac contraction then is small. Calcification of the exudate is seen occasionally.

Complete surgical decortication by removal of that portion of the pericardium and the organized exudate which lies upon the epicardium of the ventricles will restore an essentially normal cardiac mechanism. In seriously ill patients this should be accomplished in two partial stages in order to permit gradual adjustment to the physiologic changes.

Mitral Stenosis

Pathologic Changes. Mitral stenosis is the most common of the late sequelae of rheumatic fever. The thickening and fibrosis characteristic of chronic rheumatic valvulitis in part derive from intrinsic changes occurring within the substance of the valve and in part from the organization of vegetations and exudate on the surface of the leaflets especially over the "zones of contact" (during ventricular systole). The exudate becomes heaped up at the poles or "angles" formed by the junction of the leaflets (Figure XVII-10A, B). In more severe cases, exudate also may envelop the chordae and the papillary muscles like a coating of ice upon the branches of a tree, tending to "fillet-in" the angles formed between adjacent structures. Subsequent invasion by fibroblasts converts this exudate into a thin coating of fibrous connective tissue which, as the process may be repeated, gradually leads to the accretion of successive layers of scar tissue upon the valve and to more extensive subvalvular alterations.

Cross-fusion of leaflets. Cross-adherence of the valvular leaflets begins at the "commissures" or sites of folding of the normally continuous valve ribbon and progresses centripetally. A late factor which finally increases the rate of valvular narrowing is the mechanical trauma which the necessarily increased velocity of blood flow through the diminished orifices imposes upon its margins (Rodhard, 1952; reported, 1953).

Subalveolar changes. The chordae tendin-



Figure XVII-10A. Normal mitral valve (From Bailey, *Surgery of the Heart*, 1955, courtesy of Lea and Febiger.)

ae may become clumped into cable-like structures by the enveloping scar tissue. The organization of sheets of fibrin which may extend from the free margin of the leaflets over the mesh of attaching chordae, can eventuate in a "lengthening" of the leaflets, with consequent apparent shortening of the chordae (Brock, 1952). In many cases one or both of the papillary muscles may become directly adherent to the apex of a "lengthened" valve (Figure XVII-11A-D).

Valvular calcification. In about 39 per cent of cases of mitral stenosis (Bailey, 1955), calcific changes become superimposed upon the distorted valve. In general, we recognize three types of valvular calcification: (1) sand-like loosely attached encrustations which readily may become dislodged and cause arterial embolization, (2) intrinsic (subendothelial) calcification in which the leaflets become hardened, and (3) dense, block-like masses of calcific material which distort the orifice of the valve.

Intra-atrial thrombosis. Atrial fibrillation is seen in approximately 50 per cent of the patients who seek surgery for mitral stenosis (Bailey, 1955). Once this functional impediment to evacuation of the atrium becomes added to the factors of damaged endothelium and stagnation of flow, the tendency toward intra-atrial thrombosis becomes marked. Us-



Figure XVII-10B. Heaping up of fibrinous exudate at valve pole owing to incessant separation and approximation of the leaflets. (From Magarey, courtesy of *British Medical Journal*, 1:856, 1951.)

ally, thrombosis is limited to the left atrium but it may occur also within the right atrium, especially if tricuspid stenosis coexists. Atrial thrombosis is found in 25 per cent of patients with mitral stenosis, chiefly in association with atrial fibrillation.

Pulmonary vascular changes. The increased intra-atrial pressure resulting from the valvular obstruction is transmitted through the directly continuous valveless pulmonary veins to the pulmonary capillaries, disturbing the osmotic balance and threatening to produce pulmonary edema. The early development within the arterioles of medial thickening and intimal hyperplasia is followed by adventitial and medial fibrosis, and finally by irreversible luminal obliteration or frank thrombosis. The earlier vascular changes may undergo resolution if effective surgical relief of the valvular obstruction is provided.

Closed Technique of Surgical Treatment. Following the suggestion of Sir Lauder Brunton (1902) that the diminutive valve slit should be lengthened in a linear fashion, Bailey in 1918 (published in 1949) deliberately incised the "anterolateral commissure"

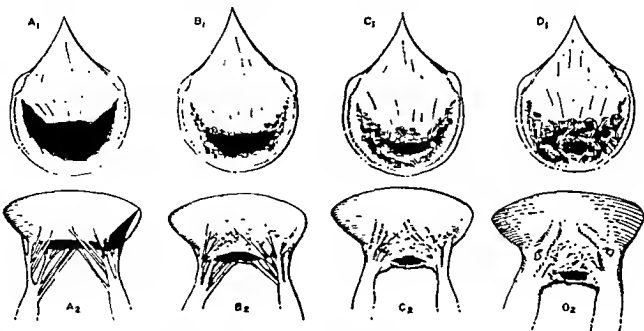


Figure XVII-11. Successive stages in development of mitral stenosis.

- A_{1, 2}. Vegetations on the (atrial) zones of mutual leaflet contact
 B_{1, 2}. Beginning cross-fusion of the leaflets at commissures. Beginning organization of fibrin deposited upon the "zones of contact." Fibrin enveloping chordae tendineae and "filling-in" all angles formed by their junction with the leaflets and with each other
 C_{1, 2}. Valve orifice reduced to a nearly straight slit. Organization of subvalvular "webs" of fibrin.
 D_{1, 2}. Valve opening diminished to a tiny round or oval aperture. Leaflets "elongated" and papillary muscles partially "absorbed," owing to organization of the fibinous exudate which has been deposited upon the free margins of the valve leaflets and upon the chordopapillary structures.

of a severely stenotic mitral valve with a hooked knife passed into the left atrium along the palmar aspect of the right index finger by way of an incision made in the purse-stringed tip of the auricular appendage. Subsequently it was realized that in favorable cases the fused valve commissures can be split or "fractured" by digital pressure alone. This operative procedure has been termed *mitral commissurotomy*, valvulotomy, valvotomy, or valvuloplasty. The procedure has been accepted generally and employed extensively for the relief of severe mitral stenosis. Unfortunately it does not provide maximal relief of the obstruction and not infrequently the benefit is lost owing to recurrence of stenosis (Bailey *et al.*, 1957).

While this technique has benefited many patients, it seems probable that it soon will be replaced by the newer technique of "neostrophlingic" (Greek: *neo*-new; *strophlings*-hinge) mobilization (Bailey *et al.*, 1958) of the valve along the nearly semicircular "line of closure" which is based upon a better

understanding of the pathologic anatomy and physiology of the stenotic mitral valve. To accomplish such mobilization, either instrumental incision (79 per cent of cases) or digital "splitting" may be used, frequently in combination. The "concave" mural leaflet, being short from free margin to base, usually will have become totally involved and completely rigid. Restoration of mobility to such a leaflet presently is inconceivable. However, valvular function of a unicuspid type can be imparted once the "longer" septal leaflet has been "re-hinged" upon its characteristically flexible mid-zone. Such a unicuspid flap-valve mechanism (Figure XVII-12A, B), while not entirely normal to the human mitral valve, is the natural mechanism of action of the mitral valve in some of the lower vertebrates. Furthermore, an efficient mechanism can be established in nearly every case of mitral stenosis. This type of mobilization can be accomplished consistently only when the technically more advantageous right-sided thoracic approach is used.

Relief of Subvalvular Stenosis. Subvalvular "secondary" stenosis may be relieved in most cases by splitting the papillary muscles with end-on pressure with the finger tip. If this maneuver fails, the apex of the fused chordopapillary mass may be divided by special scissors, the papillary incision then being extended by digital pressure.

Summary of Experience with Closed Technique. The technique of neostrophing mobilization of the mitral valve by way of the right thoracic approach has proved generally satisfactory. The over-all operative mortality in more than 600 patients operated upon by this method has been approximately half (4 per cent) of that experienced with the older operation (left-sided approach). Moreover, complete relief of the stenosis is obtained in most patients. The diastolic murmur of mitral stenosis has been abolished in more than half of the patients.

Surgical Treatment with Cardiopulmonary Bypass. Open surgery for mitral stenosis has been disappointing in most clinics. Partly because of the deep posterior location of the left atrium, direct visualization of the atrial aspect of the mitral valve is none too satisfactory, and its ventricular aspect, the annu-

lus fibrosus, and the chordopapillary supports are entirely hidden. Therefore, it still is necessary to perform the operation on the non-functioning valve essentially by guidance of the sense of touch. Because of fear of producing severe mitral regurgitation (which he cannot easily recognize or evaluate in the poorly functioning valve), the surgeon is constrained to restrict the extent of valvular mobilization to less than the ideal limits.

In instances of borderline operability, the closed technique may be rendered easier for the patient to bear and therefore safer, by using a "heart-lung" apparatus to support the circulation. The venous return is removed from the right atrium by a large catheter inserted through an incision made in the auricular appendage. After oxygenation, the blood is returned to a systemic artery. By this means, the left atrium is rendered smaller and the surgery may be carried out methodically, without risk of sudden circulatory failure. At any time, in order to assess the extent of restoration of function or the possibility of creation of any incompetence, the full circulatory load may be returned to the valve by slowing or stopping the mechanical pump.

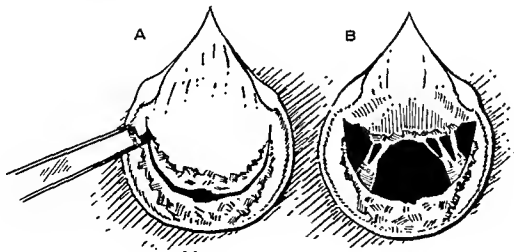


Figure XVII-12. Mitral stenosis.

A. Arcuate line of closure of stenosed mitral valve as seen in supine posture. Coul-taine is applied and the original line of valve cleavage is opened anatomically and slightly beyond the normal anatomic limits, to sever the fibrous bridges at either valve pole.

B. During diastole, the longer septal leaflet "bends in the middle," providing an efficient unicuspid "flap-valve" action. The shorter mural leaflet usually will have degenerated into a completely rigid fibrotic or calcific arcuate shelf which can never move again.

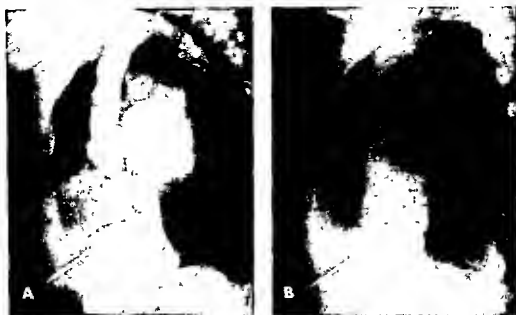


Figure XVII-13. Proof of the existence of mitral valve incompetence and a rough quantitation of its magnitude may be obtained by ventriculography.

A. Preoperative ventriculogram obtained from patient with severe mitral regurgitation. Opacification of the left atrium nearly equals that of the aorta.

B. Ventriculograms obtained in same patient 6 weeks after Nichol's procedure. Note lack of opacification of left atrium, indicating a high grade of correction of the insufficiency (From Nichols, *Journal of Thoracic Surgery*, Vol. 33, courtesy of C. V. Mosby Co.)

Mitral Insufficiency

Surgical Pathology. Mitral regurgitation often is combined with an element of mitral stenosis since it may be the end-product of similar changes. We may have "pure" stenosis, "pure" regurgitation, predominant stenosis with less significant regurgitation, predominant regurgitation with less significant stenosis, or relatively equal degrees of involvement. Other than in posttraumatic cases, there are but three basic types of mitral regurgitation: (1) congenital deformity of the valve, (2) dilatation of the left atrioventricular annulus fibrosus, and (3) shortening or retraction of the mitral leaflets. Insufficiency is most likely to appear in the region of the posteromedial extremity of the "line of closure" where the normal systolic overlap is least (Chiechi and Bailey, 1954).

Pathophysiology. With each cardiac contraction, a portion of the blood within the left ventricle is expelled into the left atrium, distending it and producing a characteristic pressure wave. With any reduction in the stroke output, a larger-than-usual proportion of the

ventricular content is delivered into the relatively low-tensioned left atrium rather than into the higher-tensioned aorta. Thus, the coronary arteries are less well perfused at the time of the most critical need. Because of this basic circulatory instability, as well as the advanced degree of myocardial deterioration which these patients often present, closed operations for mitral insufficiency carry a greater risk than those performed for mitral stenosis.

Diagnosis. Injection of isotopes, use of dyes, and measurements of pressure by catheterization of the right and left sides of the heart have not, in our hands, proved helpful in grading mitral insufficiency. We feel that the best method of establishing the approximate degree of mitral regurgitation is the radiographic technique of ventriculography developed by Beato-Nunez and Ponsdomenech (1951), Smith and associates (1954), Lehman and associates (1957) and Ravitch (see Wilder *et al.*, 1957) (Figure XVII-13A, B).

Closed Surgical Method of Treatment. Of the many closed surgical techniques which

have been proposed for the alleviation of mitral regurgitation, only the technique of polar plication of the annulus fibrosus which was devised by Nichols (1957) appears to be uniformly and permanently effective (Figure XVII-14A-C). Heavily calcified valves and those which are incompetent owing to congenital malformation or previous surgical trauma, usually are not amenable to this corrective technique.

Polar Cross-Plication of the Annulus Fibrosus with the Aid of Cardiopulmonary Bypass. Lillehei (see Lillehei *et al.*, 1958), Merendino (1957), and Kay and Nogueira (1958) have modified the Nichols' procedure, using an open operative technique to accomplish a similar type of annular plication. Nichols prefers the method of closed surgery with sub-total cardiopulmonary bypass (withdrawing blood from the right ventricle and returning it, after oxygenation, to a systemic artery) in patients whose poor general condition indicates the need for circulatory assistance during the actual operative procedure.

Effler and associates (1958) and Lillehei and associates (1958) have described methods of partial leaflet replacement with prosthetics, using an open technique.

Aortic Stenosis

Aortic stenosis may be congenital or acquired. It is one of the commoner sequelae

of rheumatic fever. In approximately 50 per cent of patients rheumatic lesions of the mitral valve coexist (Bailey, 1955). Rheumatic aortic stenosis is characterized by commissural obliteration and usually by calcification (90 per cent) which tends to involve both the fused commissures and the concave aspects of the cusps.

Pathogenesis of Rheumatic Aortic Stenosis. Obliteration of the commissures as a result of organization of exudate which "bridges" the "angles" formed by the adjacent cusps begins peripherally and progresses centrally. If symmetrical, this process gradually reduces the valve opening to a tiny equilateral triangle (with a residual central incompetence). More often, the process is asymmetrical, one or two commissures remaining relatively unfused. The resultant residual valve opening then becomes a slit (usually competent) rather than a triangle (incompetent). The cusps become thickened and often retracted, owing to organization of superficially deposited fibrinous exudate.

Pathophysiology. As the reduction in the size of the valve orifice approaches a critical level (as calculated from data obtained by catheterization, about 0.5 sq. cm.), signs and symptoms of aortic obstruction develop (Goldberg *et al.*, 1956). The necessity for propelling at least a minimally adequate amount of blood through the continually di-

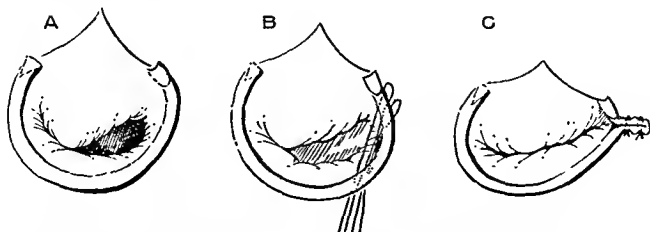


Figure XVII-14. Correction of mitral regurgitation by polar cross-plication of the annulus.

A. Diagrammatic illustration of mitral valve incompetent in region of postero-medial pole.

B. Heavy mattress sutures applied through the annular tissue in the region of the incompetent pole.

C. Tying these sutures brings the bases of the shortened cusps into closer proximity so that the free margins can make systolic contact, thus correcting the regurgitation.

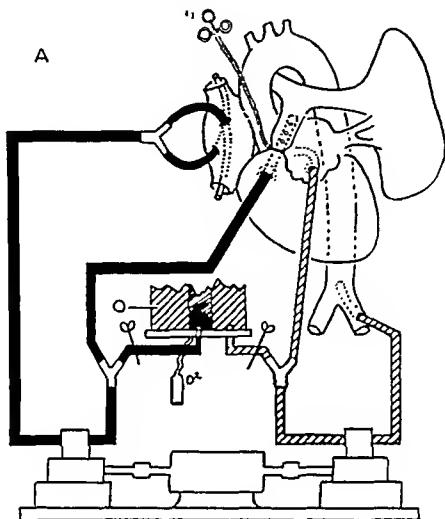


Figure XVII-15A. Diagrammatic representation of Blanco's system of circulatory bypass which employs patient's own lungs for oxygenation. O represents auxiliary oxygenator for emergency use only.

minishing aortic aperture causes the left ventricle to undergo great "concentric" hypertrophy, marked thickening of the walls occurring with little or no enlargement of the chamber. Because of the low pressure-head within the first portion of the aorta, the efficiency of coronary perfusion is impaired. In the presence of overwork of the left ventricle and great hypertrophy of its muscle, a state of relative coronary insufficiency readily develops.

The development of catheterization of the left side of the heart by Bjork (1953; published, 1954) and its popularization in this country by Fisher (1954; see Kent *et al.*, 1955) and Bougas and associates (1955; published, 1956) have enabled us to evaluate the cardiac status of patients with aortic stenosis with considerable accuracy as well as to recognize the coexistence

of other valvular lesions. It is felt that a systolic gradient of 50 mm. mercury or more across the aortic valve is indicative of a severe grade of stenosis.

Surgical Procedures for Aortic Stenosis. Closed surgery for aortic stenosis has been practiced generally either by the passage of a dilator through the left ventricular wall or by the insertion of a finger (and instrument) through a pouch sutured to an incision made in the first portion of the aortic wall (Bailey *et al.*, 1952, 1953; Bailey and Likolf, 1955, 1957). It now is conceded generally that these techniques are inadequate and that the logical approach to this lesion is an open one. In congenital defects, hypothermia may be used. In acquired disease, cardiopulmonary bypass is preferable. Because of the pro-

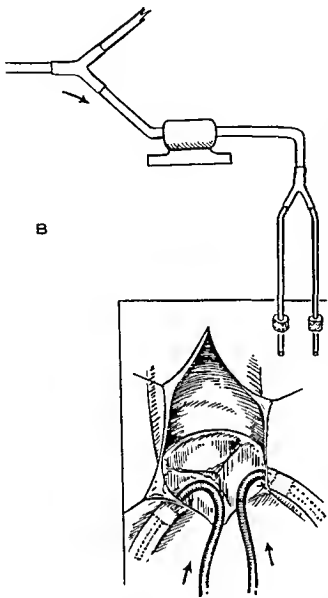


Figure XVII-15B. Direct perfusion of the coronary ostia during prolonged bypass in order to preserve the myocardial tone and vigor.

longed period of meticulous surgery that is necessary, the use of the autogenous lung (Blanco, 1957; published, 1958) is much preferable to simple artificial oxygenation (Figure XVII-15A). Direct perfusion of the coronary arteries with 100 to 200 ml. of arterialized blood per minute maintains myocardial vigor (Figure XVII-15B).

Not only may the cross-fused leaflets then be separated with critical accuracy, but loosely attached calcific fragments may be extracted with ease. In some instances, the cusps will have lost their deep cup-like configuration and then must not be detached

from their adherent and supporting fellows lest regurgitation ensue.

Gradually it has become apparent that there is a "usual" pattern to the scarring and the calcific involvement of the stenotic aortic valve. These limestone deposits are prone to develop within and beneath the fused commissures and within and upon the substance of the concave face (fibrosa layer; see Gross *et al.*, 1930) of each cusp. It would seem that the aortic cusps, like the mitral leaflets, have two faces which behave differently. The atrial face of the mitral leaflet and the concave face of the aortic valve tend to become thick and scarred and the site of calcific deposition. Contraction of the scar tissue leads to shortening and retraction of the entire aortic cusp even though the convex or ventricular face of the cusp (spongiosa layer; see Gross *et al.*, 1930), except at the commissures, tends to remain thin, smooth, and uninvolved by the calcific process.

Usually it is possible by a "sculpturing" or "thinning" technique, utilizing both sharp dissection and the use of rongeurs, to remove the concave surface of the aortic cusp without injury to the convex one. This thinning and mobilization impart both flexibility and appreciable additional length to each cusp so that both the stenosis and any coexisting regurgitation are reduced or overcome. While it may not be possible in an individual case to mobilize all 3 cusps, nearly always 1 or 2 will prove amenable to this technique. In those few valves in which the calcification does involve the convex face of a cusp, if surgical "thinning" is undertaken at all, the integrity of the endothelium of the opposite surface must be maintained by limiting the "sculpturing" to but one face (in this case, the convex one).

Aortic Regurgitation

Pathologic Changes. Incompetence of the aortic valve may be caused by dilatation of the aortic root, by distortion or prolapse of a cusp, or by shrinkage, retraction, or deformity of the cusps such as occur in rheumatic aortic stenosis. Abnormalities of the cusps may be caused by congenital deformation, trauma, rheumatic disease or bacterial endocarditis. Syphilitic aortitis and Marfan's syndrome (1896) classically produce dilata-

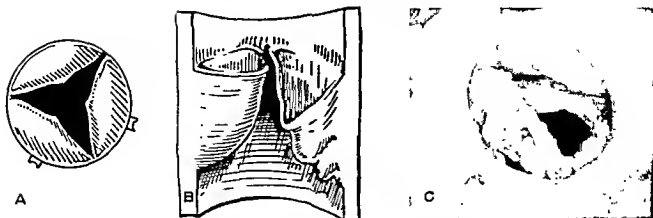


Figure XVII-16A. Symmetrical dilatation of the aortic root causes the free margins of the normal cusps to extend like geometric chords across 120° arcs of the circular aperture.

B. Prolapse or deformity of a cusp

C. Photograph showing shrinkage and deformation of aortic cusps as result of rheumatic valvulitis, causing both insufficiency and stenosis.

tion of the first portion of the aorta (Figure XVII-18A, B, C). Syphilitic aortitis may extend to the aortic valve and cause separation of the commissures with resulting aortic regurgitation.

Pathophysiology. Aortic incompetence amounts essentially to an aortico-left ventricular fistula, the size of the communication (valve area open during diastole) being a direct measure of the severity of the condition. As a result of backward flow through this fistula, the left ventricle is overworked and becomes progressively hypertrophied and dilated. The lack of diastolic guarding at the valve level causes a rapid "run-off" of aortic pressure which may approach zero by the end of diastole. Coronary perfusion, the major portion of which normally occurs during the diastolic period (Gregg and Green, 1940), now perforce must take place largely during systole. With the attendant overwork of the hypertrophied left ventricle, a state of relative coronary insufficiency readily develops.

Surgical Procedures for Aortic Insufficiency. While the insertion of a plastic ball-valve into the continuity of the descending thoracic aorta (Hufnagel, 1951) has been practiced widely in the past, it now is felt that, to be truly effective, the aortic valve must precede the take-off of the coronary arteries.

In aortic insufficiency associated with dilatation of the aortic root, the incompetent tricuspid valve may be converted into a competent bicuspid valve by a plastic operative procedure upon the first portion of the aorta, involving excision of the noncoronary cusp, which we have called "bicuspid conversion" (Bailey and Zimmerman, 1958). An open technique with cardiopulmonary or cardiac bypass is essential (Figure XVII-17A-D). Coronary arterial perfusion is desirable to maintain myocardial vigor.

For instances in which the aortic root is not dilated but in which one or two cusps are distorted or become prolapsed, another type of "bicuspid conversion" was first performed by Lillehei and associates (1958). Two of the cusps are sutured together to form a single large functionless cusp, using Ivalon sponge buffering of the suture line. The third cusp is chosen for its anatomic soundness and serves to provide a unicuspid type of valve action. While this is not as desirable as bicuspid or tricuspid valvular function, it is far preferable to valvular incompetence.

The valvular incompetence which may be associated with aortic stenosis usually can be corrected by thinning and sculpturing of the thickened cusps, as described previously, since this technique achieves an effective lengthening of the retained convex face. However, if an end-stage of the lesion precludes restoration

of mobility of the cusps, the noncoronary cusp simply may be excised, thereby relieving the stenosis. The two remaining cusps then are "lengthened" greatly by suturing, to their free margins, strips of aortic wall 1.5 cm. wide, which remain pedicled at the base of the resected cusp. By attaching the upper margins of the strips anteriorly to the arterial wall and posteriorly to the prosthetic patch which is used to repair the aorta, a functionally competent bicuspid aortic valve will be created. This may be regarded as a still different type of "bicuspid conversion" (Figure XVII-18A-C).

Tricuspid Stenosis and Insufficiency

These lesions occur not infrequently in association with mitral stenosis and even more commonly in patients with both aortic and mitral stenosis. Diagnosis of lesions of the tricuspid valve is difficult and often incorrect even after thorough physiologic study. Direct exploration of the valve by the insertion of a finger into the right atrial chamber appears to be a reliable diagnostic maneuver. Tricuspid

stenosis may be relieved by a closed procedure separating one or more of the commissures instrumentally or digitally by a technique similar to that used in mitral commissurotomy. Tricuspid regurgitation may be relieved by plication of the annulus fibrosus, such as that employed in the Nichols technique for correction of mitral insufficiency.

Atherosclerotic Heart Disease

Surgical Considerations. Atheromata tend to occur within the coronary arteries as intimal or subintimal plaques. According to Schlesinger and Zoll (1941), in the earliest phases this process nearly always is limited to the first 2 cm. of the right coronary artery and the region of the bifurcation of the left main coronary artery. Although apparently of metabolic origin and, therefore, fundamentally a medical disease, it appears that coronary atherosclerosis sometimes may be benefited by surgical intervention. Some of the procedures proposed are designed merely to relieve the pain of the accompanying angina by interruption of nerve fibers, and must

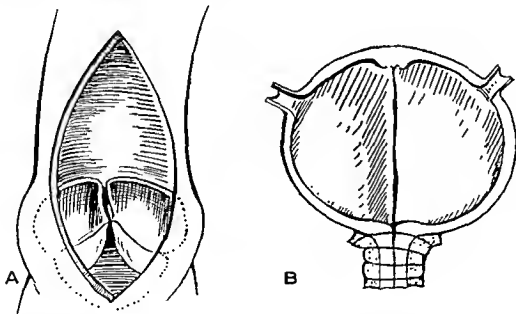


Figure XVII-17. Surgical correction of "pure" aortic insufficiency by "bicuspid conversion" of the valve.

A. An ellipse of aortic wall embracing one-third of its circumference is excised. The incision extends down into the sinus of Valsalva of the noncoronary cusp. The cusp, too, is resected but the thick fibrous line of its aortic attachment is preserved.

B. Cross-section of repaired aorta at the valve level. Note that the approximation of the commissures at either extremity of the resected cusp brings the free margins of the remaining cusps together as parallel and, therefore, contiguous diameters of the reduced circular passage.

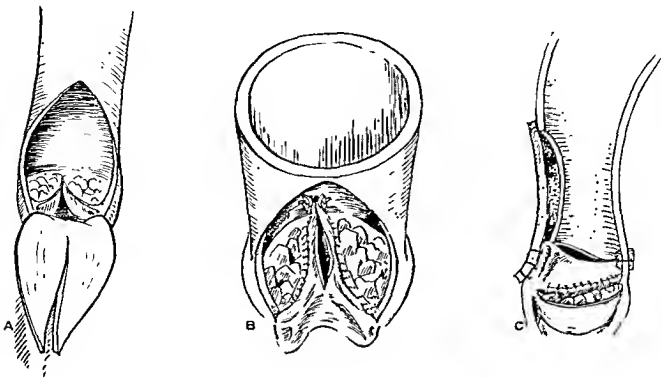


Figure XVII-18. Surgical conversion of a severely damaged, stenotic and regurgitant aortic valve into a competent and functional bicuspid one by the use of pedicled grafts of the aortic wall and excision of the non-coronary cusp.

A. The noncoronary cusp is excised and a double full-thickness flap is prepared from the aortic wall, pedicled at the site of excision of the cusp.

B. The flap is buckled posteriorly and is sutured anteriorly to the aortic wall, and laterally to the two remaining cusps in a way that lengthens them greatly.

C. Repair of the aortic wall with a water-tight prosthetic patch and attachment to it (posteriorly) of the double aortic flap.

be termed "palliative." These include the various operations for sympathectomy and for denervation of the aortic or carotid plexus.

The "physiologic" procedures for coronary artery disease are those which are intended to influence favorably the ratio of existing coronary flow to myocardial demand. In one type, comprising the various thyroid destructive operations, an attempt is made, by reducing the metabolism of the body, to lessen the myocardial demand for blood to a level which the narrowed coronary arteries can supply.

Operations for Revascularization. In other types of "physiologic" procedures, an attempt is made to increase the blood supply available to the myocardium either locally or generally. These are described loosely as "revascularizing" operations.

Stimulation of intercoronary anastomotic channels. Since an effective collateral mechanism obviously is of the utmost value in per-

mitting an efficient redistribution of the remaining coronary arterial flow in the presence of progressing atherosclerosis of the coronary arteries, it is logical that efforts should have been directed toward augmentation of the normally existing but minute "intercoronary arterial communications" by surgical means. The introduction of silicate powders (and certain other irritants) into the pericardial sac, as suggested by Feil and Beck (1941) and Thompson and Raisbeck (1942), has been demonstrated to have this effect. Ligation of the great coronary vein or subtotal ligation of the coronary sinus, as recommended originally by Gross and associates (1937), and subsequently by Beck (1941) and Fauteux (1946), has a similar and perhaps greater effect. The more risky procedure of arterialization of the coronary sinus by the surgical production of an arteriovenous fistula with the aorta and subsequent subtotal ligation

tion of the sinus, as proposed by Roberts and associates (1943), Beck and associates (1948), and Kralik (1955), has an even more profound effect in dilating the intercoronary arterioles or "loosening" the myocardial "sponge."

The combination of instillation of a silicate powder into the pericardial sac and subtotal ligation of the coronary sinus appears to stimulate a considerable augmentation of the intercoronary collaterals, thus providing a more efficient over-all distribution of whatever coronary arterial circulation remains. The surgical mortality rate of this procedure (known as the Beck I operation) is low, and the observed clinical benefit is considerable. In poor operative risks, simple instillation of silicate powder into the pericardial sac appears safer and reasonably effective.

Addition of a new source of blood to the myocardium. While Thompson (1942) believes that some additional blood supply may be provided to the ischemic myocardium by the development of vascularized adhesions between the pericardium and the surface of the heart following the intrapericardial instillation of a powdered silicate, it has not yet been possible to demonstrate an appreciable flow through them to the myocardium.

Beck's (1935) implantation of the pedicled pectoralis minor muscle upon the abraded surface of the heart, O'Shaughnessy's (1936) cardiomentopexy, and Carter's (1948) application of the left lung upon the surface of the left ventricle all were designed to bring a new blood supply from an extracardiac source to the superficial layers of the left ventricle. The not infrequent observation of infarction of the deeper layers of the left ventricular wall (subendocardial necrosis) in the presence of a more superficial overlying layer of apparently normal myocardium would suggest a fallacy in this type of surgical reasoning unless some measure were to be taken simultaneously to augment the minute interarterial communications which normally extend between the various layers of the spiral muscles.

Vineberg's (1946) suggestion that the left internal mammary artery be mobilized and

divided and that the open bleeding end of the upper segment be implanted within the thickness of the left ventricular wall, appears to offer an effective method of bringing a new source of blood to the ischemic myocardium. While the grafted artery gradually does undergo luminal obliteration when implanted into the myocardium of normal dogs (Nephtune; see Angulo *et al.*, 1953; Bakst *et al.*, 1955), it remains open and functional when the heart of the experimental animal is rendered ischemic either by minor coronary ligations in multiple stages or by gradual occlusion of the major branches.

Endarterectomy. Since atheromatous plaques forming within the coronary arterial system tend early to be of limited and segmental distribution, it was suggested by May (1956, see Bailey *et al.*, 1957) that they might be removable by endarterectomy. Radiographic demonstration of the coronary pattern by Arnulf (1957), Dotter (1957), Lehman and associates (1957), and Lemmon (1957) offer great promise for more accurate diagnosis and localization.

Direct coronary endarterectomy was undertaken by Bailey (on October 20, 1956), a specially designed curette being passed upward (from the apex of the ventricle toward the base) through an incision made in an "expendable" branch of the left anterior descending coronary artery to remove a partial obstruction located near the origin of this vessel. Prolonged postoperative heparinization has proved necessary to prevent subsequent thrombosis of the coronary artery at the site of such intimal traumatization. Up to the time of this writing, 8 such operations had been performed without an early death; 1 patient died 7 months after surgery. Six of the patients appeared objectively to have been improved.

Alternatively, endarterectomy may be performed by insertion of a curette or specially designed instrument through the normal coronary ostium (successfully accomplished by Bailey on November 13, 1957). This necessitates wide aortic incision and cardiopulmonary or cardiac bypass, preferably with coronary perfusion. Local heparinization by

means of a polyethylene tube introduced through the aortic wall is used to prevent postoperative thrombosis at the site of intimal traumatization. With this latter method, one has the advantage of a more flexible surgical technique (since all 3 major coronary arterial branches may be approached by way of their ostia) and the use of a somewhat larger instrument. Longmire (1958) has opened the coronary artery directly in order to perform endarterectomy. Conceivably, it may also be feasible in the near future to operate in this fashion on an emergency basis for acute coronary occlusion, both the thrombus and the atheromatous plaque being extracted simultaneously ("thrombo-endarterectomy") before irreversible necrosis of the ischemic myocardium has taken place.

Ventricular Aneurysm

True Ventricular Aneurysm develops upon a site of myomalacia, generally that resulting from acute coronary occlusion. The scar of a healed myocardial infarct always is much thinner than the original ventricular wall, but usually is tough and leathery, well capable of tolerating the intraventricular pressure. In a minority of cases, generally estimated at about 10 per cent, but thought by some to be as high as 20 per cent (Schlieter *et al.*, 1954), the scar is not strong enough to tolerate the continuously repeated build-up of intraventricular tension, and bulges to form an aneurysm.

Death usually occurs in ventricular aneurysm within 3 years, generally from heart failure or from arterial embolism secondary to mural thrombosis. Actual rupture is rare. Persistence of a severe anginal syndrome and the extreme restrictions in physical activity which are imposed by the small myocardial reserve, render these patients distressful during their limited period of remaining life. The loss of cardiac reserve is related chiefly to the paradoxical distension of the semi-elastic aneurysmal sac which occurs during ventricular systole, and its collapse during diastole.

Subtotal resection of postinfarctional aneurysm of the left ventricle (Likoff and Bailey, 1954; published, 1955) usually results in dramatic and persistent clinical improvement.

First, one should explore the interior of the left ventricle by passing a finger through the mitral valve (by way of the purse-stringed left auricular appendage) in order to establish the presence or absence of mural thrombus within the aneurysmal sac. If present, it may be expelled by a "flush-out" technique in which the fundus of the aneurysm is widely incised while dentate hemostatic clamps are in place but unclamped.

It is essential in these cases that no attempt be made to excise the entire area of scarring lest the ventricular capacity be reduced below minimal requirements. Only the dilated or bulging portion of the aneurysm should be resected. This technique has been called "ventriculoplasty," the ventricle merely being "tailored" to an appropriate size and shape. Alternatively, an open technique may be employed, if necessary.

False Ventricular Aneurysms may develop following trauma by penetrating wounds or a surgical ventriculotomy. In these cases, the sac usually is "false," being formed from thickened pericardium or other contiguous adherent tissues. The communicating neck between the aneurysm and the ventricle usually being small, the patient experiences relatively little physiologic handicap. In these cases, however, the risk of progressive enlargement and eventual rupture of the sac is considerable and justifies surgical correction. This has been accomplished successfully (Bailey, 1956; see Smith *et al.*, 1957) as follows: The small ventricular communication is tamponaded by a finger inserted into the lumen of the aneurysm by way of a purse-stringed incision made in its fundus. The sac is cut away and the communicating fistula is closed by the passage of sutures beneath the tamponading finger.

Congenital Diverticulum of Ventricle. Diverticulum of the ventricle may be regarded as a ventricular aneurysm of congenital origin. These rare outpouchings from the ventricular lumen cause little or no physiologic difficulty. They appear as obliquely directed pulsating masses beneath the skin of the epigastrium which can be demonstrated by opacification-radiography to communicate with one or

both ventricles. Rupture and death during infancy or childhood is the usual outcome. The surgical treatment consists of simple amputation and repair distal to a noncrushing clamp.

Neoplastic Disease

Primary or secondary malignant tumors of the heart rarely are amenable to surgical removal except in the case of local extension from a bronchiogenic carcinoma. Benign tumors of the heart often may be excised, with cure. Of these, the commonest and most important is the so-called myxoma or "cardioma" (Stout, 1955) of the atrium. This usually pedunculated lesion, of controversial origin, arises within the atrium (usually the left) from the margin of the fossa ovalis. As it grows, it extends down toward the orifice of the respective atrioventricular valve and may produce the usual evidence of stenosis or in-

sufficiency of that valve (Likoff *et al.*, 1954).

A myxoma of the right atrium may be removed by simple atriotomy while the venae cavae are obstructed temporarily, preferably with the patient under hypothermia. Similar lesions occurring within the left atrium can best be removed under normothermic conditions by an open technique with the aid of cardiopulmonary bypass (Crafoord, 1955). Nichols (1956) has devised a closed method for removal, if their presence has been unsuspected prior to surgical exploration for supposed mitral disease. A "net" of nylon upon a snare-type of instrument passed into the atrial cavity is used to entrap the tumor before detaching its pedicle with the intra-cardiac finger. The enveloped mass then is extracted from the atrium, the encased material being morcellated and deformed if the tumor is too large for intact removal by way of the appendageal (or atrial) incision.

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Gross Examination of the Heart

Injection of Coronary Arteries

Weights and Measurements of Heart

OTTO SAPHIR

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*Non vi sed arte.**

GROSS EXAMINATION OF THE HEART

THE GROSS examination of the heart is only a part of the complete autopsy, and subsequent histologic examination must be carried out in the elucidation of the morphologic changes produced by disease and their influence in the causation of death. While it is essential to make a careful examination of the exterior of the body, the serous cavities, all the organs, and the peripheral vascular bed, only the technique of opening and dissecting the heart will be considered here. Of the several methods, only one will be described in detail, and two others will be mentioned briefly. Extensive experience points to the importance of opening the heart in conjunction with the lungs and great blood vessels. Thus, the aorta must be opened in continuity with the aortic valve and left ventricle, and the pulmonary trunk in continuity with the right ventricle, pulmonary valve and lungs. Although such a

dissection in conjunction with adjacent structures may be cumbersome, a number of details are likely to be missed if the heart is separated from the rest of the organs and examined alone.

The following instruments are recommended for dissection of the heart: a knife with a long-bladed single cutting-edge, often called an amputation knife; an enterotome; a small dissecting scissors, to open the branches of the coronary arteries; one or two pairs of forceps; and several hemostats and a probe.

If a blood culture is desired, the sample of blood should be removed from the heart at the beginning of the autopsy. The pericardial sac is incised and the ventral surface of the right atrium cauterized with a hot spatula. The blood for culture of organisms is drawn from the right atrium with a sterile needle

* "Not by force, but by art." From *Iliad*, Book 23.

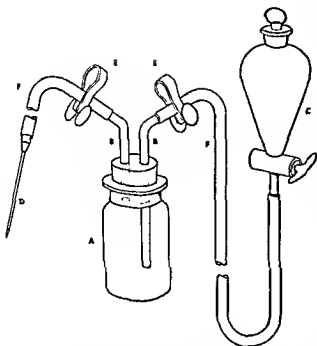


Figure XVIII-1. A device by Kulka for demonstrating air embolism. (From Kulka, W. A practical device for demonstrating air embolism. *Arch. Path.*, 49:360-369, 1949. Courtesy of *Archives of Pathology*.)

and syringe, or with a pipet. Gentle pressure upon the liver will aid in obtaining the sample.

In the following discussion, it is assumed that the autopsy has progressed to the stage where it is possible to remove the heart, large vessels, lungs and the ascending aorta *en masse*, after cutting the descending aorta just above the diaphragm. These organs are placed on the autopsy table with the ventral surfaces of the lungs and heart in the immediate view of the prosector, the arch of the aorta being directed away from him. As stated above, the heart during its dissection must be left in continuity with the adjacent structures. The pericardial sac is now opened by means of scissors, if it has not previously been opened, in order to take a specimen of blood for culture. It is incised in the region of the apex of the heart and a triangular flap is cut in the ventral portion of the parietal pericardium, the flap corresponding roughly to the size of the ventral wall of the heart. This flap is reflected cephalically from the heart but left attached to the aorta in the region of the reduplication of the pericardium. Care must be taken to observe the type and amount of fluid which is present within the pericardial cavity.

Before opening the heart it is sometimes imperative to ascertain the presence of air or fat emboli in the right ventricle or pulmonary trunk. To demonstrate air emboli, water is introduced into the pericardial sac, the incised sac being held taut with hemostats or forceps applied to its cut edges. The right atrium may now be opened under water and the escape of air bubbles observed. Minute air bubbles, indicating postmortem decomposition, are almost constantly noted. If facilities are available, it is better to immerse both the heart and the lungs in a deep pail of water. Thus, the pulmonary trunk can be opened under water, and slight pressure upon the right ventricle will allow the escape of air from the ventricle. Fat emboli might also be demonstrated.

Air Embolism. A practical device for demonstrating air embolism was recommended by Kulka (1949). This method can be used for quantitative and qualitative demonstration of air or other gases that may be present in the cardiac ventricles.

Figure XVIII-1 shows the apparatus for the demonstration of air embolism. The apparatus consists of the following parts:

A. A wide-mouthed glass bottle of 2- or 3-ounce (60 to 90 ml.) capacity, fitted tightly with a two-holed rubber stopper.

B. Two sections of glass tubing with an inside diameter of approximately 3 mm., each section being bent at an angle of 120 degrees. One of these sections should be longer than the other. The shorter one should reach just through the stopper and be even with the inner surface of the stopper. The longer one should reach to within 1 or 1.5 cm. of the bottom of the flask. Both tubes should fit tightly into the holes of the stopper.

C. One separatory funnel (pear-shaped and of 60- to 100-ml. capacity) connected to the longer section of bent glass-tubing by rubber tubing 100 cm. in length (F). An amber, pure-gum rubber tubing, such as is used on blood diluting pipets, has proved satisfactory.

D. One transfusion needle, No. 14 or 15 gauge, 4 or 5 cm. in length, connected to the shorter glass tube by a short section of rubber tubing not exceeding 5 cm. in length (F).

E. Two pinchcock clamps, one for each length of tubing. They may be of the spring type or of

the household-syringe type. The latter will prove advantageous if the gas collected is to be transported for analysis.

The entire system is filled with liquid petrolatum so that when the funnel is at a level with the upright bottle the oil fills about one-half of the funnel.

Technique. In operation the funnel is first raised to a position 30 or 40 cm. above the level of the upright bottle. All the stopcocks are opened and the position is retained until every trace of gas has been driven from the system through the needle which is thereby coated on the inside by a film of oil. After all air has been expelled, the stopcocks are closed and the funnel lowered once again to its original position.

As a precautionary measure and control, the airtightness of the whole system should be tested before operation. This is done by inserting the needle into musculature or skin and attempting to induce aspiration in the following manner. The bottle is inverted and the needle inserted into the cavity in question. When the needle is in position, all stopcocks are opened. The funnel is lowered about 70 to 90 cm., or until adequate suction is created. The contents of the cavity are thereby aspirated. The contents may be air or other gases, either pure or mixed with blood or other liquid. Any gas or liquid entering this system may be observed through the wall of the short bent glass-tubing. If the test is positive, gas bubbles will collect in the bottle above the level of the oil. If desired, this gas may now be saved for further examination by closing all the stopcocks and returning the bottle to its upright position.

Opening the Heart. The heart is now lifted up from the posterior parietal pericardium, and held with the left hand in such a fashion that, if normal in size, it is almost completely encircled, the four fingers and the palm encircling the right ventricle, the thumb partially encircling the left ventricle. The heart is rotated about 90 degrees so that its left margin (margo obtusus), exposed between the thumb and the tips of the fingers, faces the prosector. The long knife, held in the right hand, now cuts the left ventricle along its left lateral margin (Figure XVIII-2). The four fingers of the left hand are now inserted into the left ventricular cavity through this cut and the ventral wall of the left ventricle is held between the thumb and the four

fingers. The apex is raised from the table and the heart tilted so that the line of the margo obtusus forms an angle of about 90 degrees with the aorta. A large knife (amputation knife) is held near the end of the handle and loosely between the thumb, index and middle fingers of the right hand, and made to pierce the apical portions of the wall of the right ventricle at its lateral margin (margo acutus) and penetrate the right ventricle. It is directed through the right ventricular cavity and through the tricuspid orifice and pierces the right lateral wall of the right atrium from within, the tip of the knife emerging through its lateral margin (Figure XVIII-3). These openings in the right ventricle and right atrium are connected by splitting open the right ventricle along its lateral margin (margo acutus), with the blade of the knife resting in the right ventricle. This incision is made from within the ventricle and atrium. It exposes the right ventricular cavity and a portion of the right atrium and cuts through the tricuspid valve along its right lateral margin. The

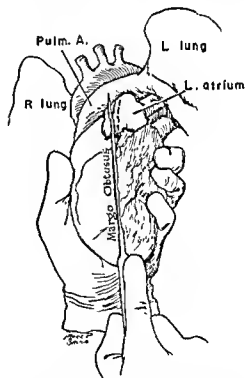


Figure XVIII-2. Diagram showing method of first incision, along the left lateral margin of the left ventricle. (Figures XVIII-2 to XVIII-10, reproduced by courtesy of Paul Hoeber Co.)

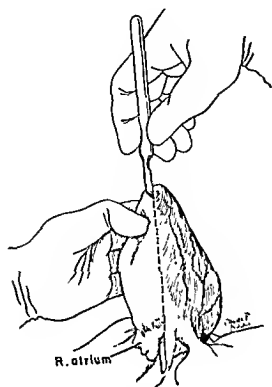


Figure XVIII-3 Diagram showing the path of the incision along the lateral margin of the right ventricle. The blade cuts from within the ventricle and atrium

heart is now again placed in its normal position and the blunt blade of an enterotome is introduced into the right atrium which is completely opened by continuation of the ventricular incision. From the atrium the enterotome is also inserted into the superior and inferior *venae cavae*, both of which are now opened by continuing the atrial incision. The presence or absence of an open *foramen ovale* may be ascertained now.

The *pulmonary valve* and the *pulmonary trunk* are exposed next. The heart is maintained in its normal position. The four fingers of the left hand are placed into the right ventricular cavity and the ventral wall of the right ventricle is held between them and the thumb. With the enterotome directed by the right hand, an incision is made through the wall of the right ventricle, producing a roughly triangular flap (Figure XVIII-4). This incision starts at the apex, extends very close and parallel to the interventricular septum and cuts through the pulmonary valve and the pulmonary trunk. After completion of this in-

cision, the opened pulmonary trunk is immediately examined for the presence of an embolus. For this purpose the vessel is carefully washed with a stream of water. If there is a patent *ductus arteriosus*, it may also be noted now. The right chambers and the tricuspid and pulmonary valves are now examined. It is imperative to look for mural thrombi in the right *auricular appendage*. In this examination it is recommended that a small portion of the sharp edge of the appendage be cut with scissors from the outside, and the inner wall examined through this incision.

Completion of the opening of the left side of the heart follows. The left ventricle was previously opened along its lateral margin. The index finger of the right hand is now introduced into the left atrium through the mitral valve to palpate for evidence of stenosis of its orifice. If the orifice is stenotic a different procedure is indicated which will be referred to later. If stenosis is not manifest, the blunt blade of the enterotome is introduced through the mitral valve into the left atrium and both the valve and the atrium are cut open along the left lateral border of the heart by continuing the line of the first incision made to open the left ventricle. Care must be taken, in making this incision, that the end of the enterotome is directed through the mitral orifice and not through the aortic orifice. After the left atrium is exposed the *pulmonary veins* which enter into it should be opened and inspected. The presence or absence of a *foramen ovale* has been previously ascertained.

The next and most difficult incision exposes the *aortic valve* and the ascending aorta. The heart is placed in its normal position. It is wise first to insert the index finger of the right hand through the aortic valve to determine if its orifice is stenotic. If stenosis is found, a different procedure is indicated. This will be mentioned later. If there is no stenosis, the four fingers of the left hand are placed in the cavity of the left ventricle. The ventral wall of the left ventricle is held between them and the thumb which should be in contact with the ventral surface of the left ventricle (Figure XVIII-5). This position appears

somewhat awkward, since during the next incision the left hand, holding the flap cut from the ventral wall of the left ventricle, is placed above and across the right hand. The blunt blade of the enterotome, held in the right hand, is introduced into the left ventricle and the ventral wall of the left ventricle is incised, the incision extending cephalically from the apex, parallel to and close to the septum through the aortic valve and into the ascending aorta. This incision of necessity cuts through the pulmonary trunk which is transected above the pulmonary valve, care being taken that this valve is not injured. Such injury is avoided if the line of incision is directed just between the left auricular appendage and the outer aspect of the pulmonary valve which can easily be palpated. The aorta is opened to its arch and from there along its dorsal surface. If the thoracic portion of the aorta, removed in continuity with the heart, has been previously opened, the enterotome, after opening the arch, is directed toward the line along which the descending thoracic aorta has been opened. The left ventricle and particularly the mitral and aortic

valves are carefully washed with a stream of water and may now be studied. During this procedure care must be taken not to remove thrombi which may be mistaken for clots. The latter are often yellow and elastic and are easily removed by a stream of water. Thrombi, however, are gray or dark red, attached to the wall and are not easily removable. They may be ragged or smooth. Often clots are heavily intermingled with vegetations of acute or subacute bacterial endocarditis. For means of distinguishing these, see page 713. The left auricular appendage must be examined for thrombi in a manner similar to that described for the right auricular appendage.

Procedure to be Followed in Stenosis of Valvular Orifices. Stenosis of the valvular orifices is best demonstrated in unopened valves. Therefore, in instances of *stenosis of the mitral valve* a separate incision into the left atrium up to the mitral ring should be made, instead of continuing the ventricular incision through the mitral valve. This opening into the left atrium is made along the left lateral margin of the atrium following the line of the incision made to open the left

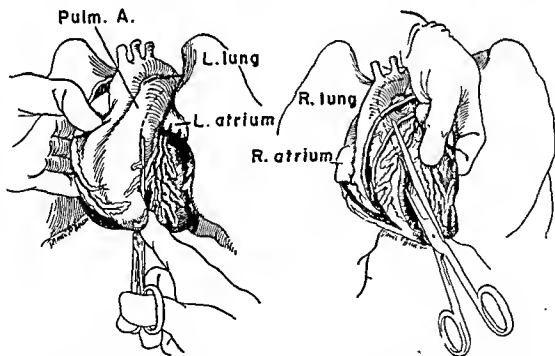


Figure XVIII-4 (left). Diagram of incision through the wall of the right ventricle.

Figure XVIII-5 (right). Incision of the ventral wall of the left ventricle. The flap cut from the wall is retracted with the left hand while with the right hand the blade is introduced into the ventricle.

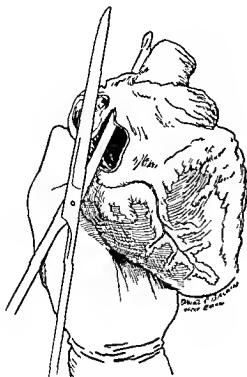


Figure XVIII-6. Incision of the right atrium of an isolated heart. The incision is made between the openings of the inferior and superior venae cavae.



Figure XVIII-7. Dissection of the isolated heart. The right ventricle is opened along the margo acutus.

ventricle. The exposure of the left atrium should be enlarged by opening the mouths of the pulmonary veins. Thus, the mitral orifice can easily be viewed. In *stenosis of the aortic orifice* the incision which goes along the septum of the left ventricle must not be continued through the aortic valve, but terminated where the base of the aortic valve comes into view. The ascending aorta is now opened, the incision starting at the termination of the incision which had been made to open the abdominal aorta; or an incision may be made into the aorta starting proximal to the opening of the innominate artery. The line of the incision must correspond to the one made to open the left ventricle to expose the aortic valve. The incision in the aorta extends up to the region of the sinus of Valsalva but does not pass through the aortic orifice. Thus, a good view is obtained of the stenotic aortic valve, the sinus of Valsalva being readily visible from the aorta and the ventricular surfaces of the aortic cusps being visible through the ventricle.

Dissection of Isolated Heart. If on rare

occasions the heart must be removed from the body and examined separately, the following technique may be used: The heart is grasped at the apex and pulled cephalically and ventrally, severing in succession, first the inferior vena cava, then the left pulmonary veins, the left pulmonary artery, the right pulmonary artery, the right pulmonary veins, the ascending aorta and finally the superior vena cava. These structures should be cut as far from the heart as possible so as not to injure the atria.

The heart is now opened and dissected only with the enterotome. It is opened in the direction of the flow of blood. In general, as Farber (1937) stated, when the scissors enter the ventricle, the apex of the heart is pointed away from the operator; when the scissors leave the ventricle, the apex of the heart is directed towards the operator. The heart is held with the left hand. On opening the atria the left hand encircles both ventricles. The enterotome is introduced first through the inferior vena cava and extends into the opening of the superior vena cava, and the right atrium is cut between the openings of these two

veins (Figure XVIII-6). In opening the right ventricle, the heart again is held with the left hand, the lateral margin of the right ventricle (margo acutus) facing the prosector, and the atria being directed toward him. The enterotome is introduced into the right atrium, through the tricuspid orifice, and the right ventricle is opened along the margo acutus (Figure XVIII-7). In opening the pulmonary valve, the heart is placed so that the apex of the heart is directed towards the examiner. The enterotome is introduced into the right ventricle close to the apex along the line of incision that has just been made and the conus pulmonalis and the pulmonary valve are cut along the interventricular septum (Figure XVIII-8). The incision should be extended into the main stem and left pulmonary artery.

Next, the left atrium is inspected, and this is done after cutting through its wall, the line of cutting connecting the openings of the pulmonary veins. An excellent view is now obtained of the inside of the atrium including

the mitral valve. Next, the left atrium is incised along its left lateral wall; the incision extends through the mitral orifice and along its left lateral wall (margo obtusus) to open the left ventricle. During this incision the ventricle is held (Figure XVIII-9) so that the apex is directed away from the examiner, and the left lateral margin of the heart (margo obtusus) is directed toward him. The next incision is designed to open the aortic valve. The left ventricle is again incised, the apex being directed toward the examiner, so that the line of incision extends from the apex (from the point reached by the incision that has just been made into the left ventricle) along the interventricular septum into the aorta, opening the aortic valve (Figure XVIII-10). In doing so, that portion of the pulmonary trunk which remained attached to the heart is pulled ventrally to avoid cutting it.

Maresch and Chiari (1933) recommended the following technique which has been the routine procedure for many years at the Vienna Pathologic Institute. The heart is opened by

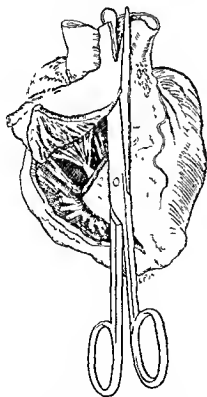


Figure XVIII-8. Dissection of the isolated heart. The conus pulmonalis and pulmonary valve are cut along the interventricular septum.

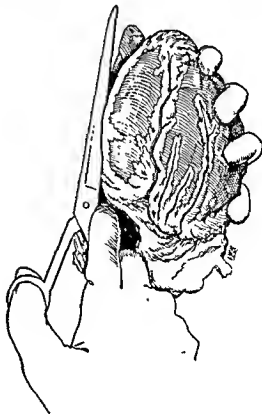


Figure XVIII-9. Dissection of the isolated heart. Incision of left atrium and left ventricle. Note position of the heart.

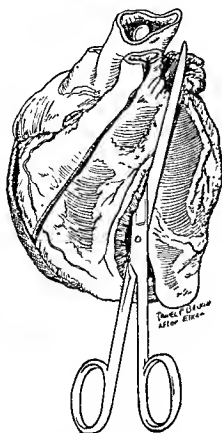


Figure XVIII-10 Dissection of the isolated heart. The aortic valve is opened by continuation of the incision shown in Figure XVIII-9

means of 4 sections with the long knife (amputation knife). It is lifted from the pericardium and incised along its left lateral border. Both the left atrium and left ventricle are opened with the long knife, the *incision into the atrium* being directed between the openings of the pulmonary veins. If the annulus fibrosus has not been opened by this incision, the mitral valve may now be opened either with the knife from within the ventricle or with an enterotome, the blade with the blunt end being introduced through the ventricle into the atrium. The *second section* opens the right ventricle and right atrium with the knife and is similar to the one previously described, the heart being tilted upward and the knife being introduced through the apex into the right ventricle and atrium, piercing from within the lateral atrial wall about halfway between the opening of the superior and inferior vena cavae. The tricuspid valve, if not diseased, is opened by this incision. The *next*

incision opens the pulmonary valve and pulmonary trunk. This is done with the knife, cutting along the interventricular septum. The ventral wall of the right ventricle is held with the left hand, the four fingers being inside the ventricular cavity, while an assistant holds the ventral wall of the left ventricle extended, to facilitate the incision. The point of the knife is directed through the ventral wall of the pulmonary trunk and cuts through the ventral wall of the right ventricle close to and parallel to the septum. The entire right ventricle, pulmonary conus, pulmonary valve and a portion of the pulmonary trunk may now be viewed. The *fourth incision*, which is designed to complete the opening of the left ventricle and to expose the aortic valve, is the counterpart of the third. The left hand holds and extends the dorsal wall of the right ventricle close to the apex (an assistant holding and extending the ventral wall of the left ventricle), while the knife or enterotome is introduced into the left ventricle and cuts close to and along the septum from the apex upwards into the aorta, opening the aortic valve. Maresch and Chiari recommended turning the knife or the enterotome (Figure XVIII-10) to the right, immediately after opening the aortic valve, so as to avoid injuring the pulmonary valve.

Gross Examination of the Myocardium. After the heart has been dissected and the heart valves and the endocardium examined, the myocardium must be scrutinized. For the presence of fatty infiltration of the myocardium, it is best to examine the wall of the right ventricle and in particular that surface which has been exposed by cutting open the tricuspid valve. Early fatty infiltration is commonly found in this region of the myocardium. For vascular disturbances and possible gross evidence of inflammation, it is best to make several cuts through the myocardium. First, the ventral flap of the left ventricle, between the lines of incisions made to open the aortic and mitral valves, is transected, the transection always extending parallel to the endocardial and pericardial surfaces. Thus the whole flap is transected. The second line of section cuts through the myocardium corresponding to the

left lateral and dorsal wall of the left ventricle and through the interventricular septum. Both of these sections should be made with the larger knife, the line of section covering as large an area as possible, and extending from the apical regions to about the level of the mitral valve. Again the incision is parallel to the endocardial and pericardial surfaces. Several longitudinal cuts may now be made through both atria and the right ventricle. It is also important to incise the interventricular septum by means of several longitudinal cuts, after which the left and right papillary muscles may be incised.

In disturbances of cardiac rhythm, and especially in unexpected deaths, the areas of the myocardium in which the conduction system of the heart is located (see Figures III-24 to III-27) should be submitted to histologic examination. The epicardial surface often presents a depression between the right atrium and the superior vena cava which corresponds to the location of the *sinus node*. The corresponding endoatrial region usually contains a little more fat than the remainder of the atrium. This node does not produce a circumscribed elevated nodule and can be demonstrated only on histologic examination.

The *atrioventricular node* (Tawara) is located within the interatrial septum just cephalad to the junction of the right atrium and ventricle, and more specifically between the ventral margin of the coronary sinus (the opening of the cardiac vein) and the region just cephalad to the attachment of the medial leaflet of the tricuspid valve. This node also is not visible. Extending from the node is the bundle of His which runs through the annulus fibrosus to the interventricular septum just beneath the membranous septum where it divides into a right and left branch. Both branches are situated beneath the endocardium of the interventricular septum. They end as small branches in the subendocardial regions of the papillary muscles and columnae carneae. Occasionally one encounters small areas of thickening or calcification just beneath the membranous septum at points of subdivision of the bundle. In extremely rare

instances a minute tumor may be found at such a point (see page 876).

Selection of Sites for Cutting Blocks of Tissue. It is important to cut a number of blocks to include the valvular endocardium, the mural endocardium and the myocardium of both ventricles and atria for histologic examination. Often the entire explanation for a seemingly complicated case is found on histologic examination of the myocardium. The blocks may be hardened in 10 per cent formalin* or in Zenker's formol.** Selection of sites for removal of blocks of myocardium is difficult. Those portions of the myocardium which grossly seem abnormal should always be examined histologically. Routinely, sec-

*"10 per cent formalin" is a 10 per cent aqueous solution of the commercial preparation of 38-40 per cent formaldehyde gas in water. Ten per cent formalin therefore represents a 4 per cent solution of formaldehyde in water. (Formula: 40 per cent formaldehyde 10 ml., distilled water 90 ml.)

**Zenker's formol (Helly's solution) consists of 90 ml. of Zenker's solution and 10 ml. of 40 per cent formaldehyde. Zenker's solution consists of 2.5 Gm. potassium dichromate, 5.0 Gm. mercuric chloride, distilled water up to 100.0 ml.

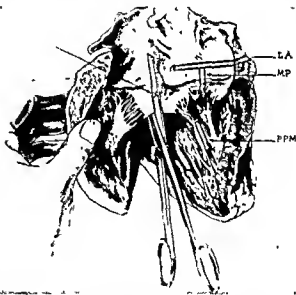


Figure XVIII-11. Diagram of left atrium and ventricle (left inflow tract) showing the method of cutting blocks from the left atrium, mitral posterior, left posterior papillary muscle, and aorta, aortic valve and mitral valve. (Taken from Gross, L., Antopol, W., and Sacks, B.: A standardized procedure suggested for microscopic studies on the heart. With observations on rheumatic hearts, *Arch. Path.*, 10, 840-852, 1930. Reproduced by permission of the authors and the publishers.)

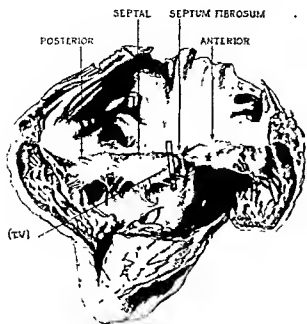


Figure XVIII-12. Diagram of the right atrium and ventricle (right inflow tract), showing the method of cutting block from the tricuspid valve and septum (T. V.). (From Gross *et al.*)

tions should be taken from the interventricular septum, from the ventral wall of the left ventricle beneath the mitral valve, and from a corresponding portion of the dorsal wall of the left ventricle. Sections from the right ventricle should include a portion of the apical region on the ventral and dorsal walls and sections from both atria should include, when mural thrombi are present, portions of the thrombi with adjacent myocardium. Gross and associates (1930) recommended that blocks be cut from the following regions of the heart for histologic examination for Asch-
 (1) *left atrium*, approximately 1 cm. above the insertion of the posterior leaflet of the mitral valve, to show the left atrial endocardium, subendocardium, myocardium and pericardium, and sometimes the coronary sinus;
 (2) *posterior mitral leaflet* with subjacent myocardium and endocardium, to show the left atrial endocardium and subendocardium, the myocardial wedge of the left atrium and the pericardial wedge of the left ventricle;
 (3) *posterior papillary muscle*, to show myocardium, the endocardial covering and sometimes the insertion of the chordae tendineae;
 (4) *area through the aorta, aortic valve and anterior leaflet of the mitral valve* including

the atrial endocardium, to show the left atrial endocardium, subendocardium, and myocardial wedge, the pericardial wedge, the root of the aorta, the aortic valve, and the sinus pocket (Figure XVIII-11); (5) *pulmonary trunk and valve*, to show the pulmonary trunk and adjacent pericardium, the pericardium of the right ventricle, the pericardial wedge, the pulmonary valve, the subpulmonic angle, the pulmonary ring and the right ventricular myocardium; and (6) *tricuspid valve*, the entire thickness of the septum and adjacent atrium, to show the right atrial endocardium, subendocardium, and myocardium, neuromuscular bundle, septum fibrosum, tricuspid ring, tricuspid valve, interventricular septum and the tricuspid pocket, and sometimes a portion of the aortic valve (Figures XVIII-11 to XVIII-16).

These 6 blocks include all 4 valves and valvular rings, the pericardium of the right and left sides of the heart, the left and right



Figure XVIII-13. Low power magnification of mitral posterior (M.P.) section. A indicates the left atrial endocardium; B, the left atrial subendocardium; C, the left atrial myocardial wedge; D, the pericardial wedge; E, the left ventricular myocardium; F, the ring of the posterior mitral valve; G, the posterior leaflet of the mitral valve, and H, the posterior mitral pocket. (From Gross *et al.*)

atria, the myocardium of the right and left ventricles, interventricular septum and left posterior papillary muscle, the bases of the aorta and pulmonary trunk, the pericardial wedge abutting against the valve rings, the neuromuscular bundle and the coronary sinus.

Note on Opening Hearts with Congenital Malformations. It is impossible to give one universally acceptable method of opening all hearts with congenital malformations. It cannot be too strongly emphasized that a heart with a congenital defect should be opened only by the experienced pathologist who, after orientation, can visualize the type of anomaly that is likely to be present in the particular instance. Only the experienced examiner can deviate from a given routine, can devise a special technique and still demonstrate all the malformations present. It is important for one not only to convince himself of the pertinent anomalies, but also to be able to demonstrate them, to retain the specimen, to photograph it and to use it for further studies. If, however, the heart is mutilated, even the prosector may be unable to demonstrate the principal anomaly. In the following description, an outline of procedures for a few given types is presented. The prosector must always be cautious in cutting, should use the probe more often than the scissors, and should inspect carefully and use blunt dissection often to clarify a complex anomaly rather than observe a too-strict adherence to the routine.

If congenital cardiac anomalies are anticipated, it is essential to remove the heart and all adjacent structures *en masse*. The ascending aorta and a portion of the descending thoracic aorta should be left in continuity with the heart, also the lungs with the pulmonary arteries and veins, the superior vena cava and its main tributaries, and the small portion of the inferior vena cava between the diaphragm and right atrium.

In general, the dissection of the heart starts with the opening of the veins and right atrium and follows the direction of the flow of blood. The mouths of the venae cavae are usually not opened. Edwards (1949) recommends a transverse incision in the ventral wall of the right atrium. Thus, the interatrial septum can

be fully examined and also the region of the tricuspid valve. If the latter is atretic no attempt should be made to force it open. The medial leaflet of the tricuspid valve should be carefully scrutinized since it may partially cover an open membranous interventricular septum. Before the right ventricle is opened,



Figure XVIII-14. Low power magnification of the aorta, aortic valve and mitral valve (A.M.V.) section. A indicates the left atrial endocardium; B, the left subendocardium; C, the left atrial myocardial wedge; D, the pericardial wedge; E, the root of the aorta; F, the aortic valve; G, the sinus pocket, H, the aortic ring, I, the subaortic angle; J, the mitral-aortic intervalvular fibrosa and endocardium; K, the mitral ring, and M, the anterior or aortic flap of the mitral valve. (From Gross *et al.*)

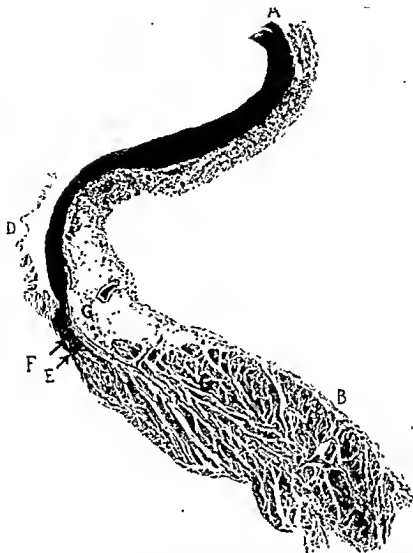


Figure XVIII-15. Low power magnification of the primary artery and valve (P.A.V.) section. A indicates the pulmonary artery and investing pericardium, B, the pericardium of the right ventricle; C, the pericardial wedge, D, the subpulmonic angle, E, the pulmonic valve, F, the pulmonic ring; and G, the right ventricular myocardium. (From Gross *et al.*)

the pulmonary trunk and aorta should be examined with respect to their size, relative positions, and region of origin from the ventricles. If at first only one vessel is found emerging from the ventricle, a search must be made for another, perhaps a small vessel, an atretic vessel or a cordlike structure close by. Before the pulmonary valve is opened, it should be probed from within the right ventricle, special care being taken that the probe actually extends into the pulmonary trunk and not into the aorta through a patent ventricular septum. The size of the *conus pulmonalis* should be determined. The *conus* may be so large as to simulate a third ventricle. After

the pulmonary trunk is opened, one glance at the sinuses of Valsalva should confirm the absence of the mouths of the coronary arteries. It sometimes happens that the scissors introduced into the pulmonary trunk will enter a patent ductus arteriosus. It must be remembered that sometimes the open ductus is equal in size to each of the pulmonary arteries and appears as a direct continuation of the pulmonary trunk. If the pulmonary trunk is narrowed or atretic, it should not be split open. Its course should first be followed and if its two branches, which are caudad to the origin of the ductus arteriosus, are of normal size or dilated, these may be opened and

through their lumina one may inspect the pulmonary trunk.

The left atrium should be opened with scissors, starting the dissection by cutting through the wall of one of the pulmonary veins and, after the incision has reached the atrial lumen, by extending the line of incision from the opening of one pulmonary vein to the others. Next, the region of the interatrial septum and the atrial surface of the mitral valve should be scrutinized. The left ventricle is opened along its left lateral margin (*margo obtusus*) and the ventricle examined immediately. It should always be ascertained at this point, if it has not been done previously, if there is a patency of the septum. A probe should be introduced into the aorta and the aortic valve examined. Sometimes the probe which is thought to be in the aorta has extended through a patency

of the septum into the pulmonary trunk or a transposed aorta. It must now be determined, before another incision is made, if there is a riding aorta carrying blood from both ventricles or a transposition of greater degree. In such instances it is best to avoid a second incision into the left ventricle. The ventricle may be viewed through the previous incision and the aortic valve, through an opening in the wall of the aorta; or an incision may be made along the ventricular septum up to the region of the membranous septum, and the root of the aorta viewed from there.

In stenosis of the isthmus, the collaterals should be demonstrated. It is also wise to seek routinely the bronchial arteries. In cases with pulmonary stenosis, this is imperative. If facilities are available, the bronchial arteries may be injected with a plastic material and the lungs subsequently macerated (see



Figure XVIII-16. Low power magnification of the tricuspid valve and septum (T.V.) section. A indicates the right atrial endocardium; B, the right atrial subendocardium; D, the neuromuscular bundle; E, the septum fibrosum; F, the tricuspid ring; G, the tricuspid valve, H, the interventricular septum, and J, the tricuspid pocket. (From Gross et al.)

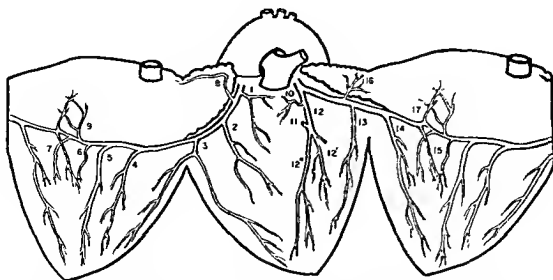


Figure XVIII-17. The distribution of the coronary arteries as found in 80 per cent of adult human hearts (over 30 years of age). (Adapted from Spalteholz.)

BRANCHES OF THE RIGHT CORONARY ARTERY

1. Arteria adiposa dextra
2. Ramus ventriculi dextri anterior
3. Ramus marginis acuti
4. Ramus ventriculi dextri posterior
5. Ramus sulci longitudinalis posterioris
6. Ramus ventriculi sinistri posterior
7. Ramus ventriculi sinistri posterior accessorius
8. Ramus atrialis dexter anterior
9. Ramus atrialis sinister posterior

BRANCHES OF THE LEFT CORONARY ARTERY

10. Arteria adiposa sinistra
11. Arteria septi ventriculorum
12. Ramus collateralis descendens anterior
- 12' Ramus primus. 12" ramus secundus
13. Ramus ventriculi sinistri anterior
14. Ramus marginis obtusi
15. Ramus ventriculi sinistri posterior
16. Ramus atrialis sinister anterior
17. Ramus atrialis sinister posterior

Hales and Liebow, 1948). According to Edwards (1949), the bronchial arteries are always removed along with the thoracic organs. When these arteries are dilated, they are easily identified as tortuous wide vessels arising either directly from the aorta, the intercostal arteries, or from the major branches of the aortic arch. It is also recommended that one inspect the relationship of the aorta to the trachea, bronchi and esophagus. The origin, course, and distribution of the coronary arteries must be examined in every instance. Abnormalities in their course may indicate transposition of the arterial trunks.

Examination of Coronary Arteries

Dissection and Distribution. The left coronary artery is opened from its mouth. The scissors are used to cut the short main coronary artery, then the anterior descending and circumflex branches and the two main branches of the latter, the ramus anterior ventriculi sinistri and the ramus marginis obtusi. The right coronary artery is opened from the point at which it was cut when the right ventricle was first incised. The artery is easily located within the coronary sulcus. First, the portion of this artery proximal to the site of

previous section is opened, to a point just short of its mouth; cutting through its mouth should be avoided to protect the wall of the sinus of Valsalva. Next, the distal portion of this artery is opened, and along with it the posterior descending branch. A number of closely spaced cross-sections of the main coronary arteries and their principal branches should be made, particularly when the coronary arteries are severely sclerosed and their lumina markedly narrowed. The advantage of this method is that very recent thrombi are not displaced. Figure XVIII-17 shows the distribution of the branches of the coronary arteries which should be opened. It is adapted from Spalteholz (1924) and uses his nomenclature. Figure XVIII-18 shows the distribu-

tion of the coronary arteries in from 5 to 17 per cent of hearts, according to Spalteholz.

Here the right coronary is the predominating artery, its terminal branch being the ramus marginis obtusi instead of the posterior descending. In about 10 per cent of cases the left coronary artery is the predominating artery, its final branch being the posterior descending artery (Figure XVIII-19). Particular care must be taken in all instances to dissect and open carefully all main branches of the coronary arteries. It is essential not to discontinue the dissection of the coronary arteries after one occluding lesion has been found but, routinely, to examine all of the main coronary arteries.

INJECTION OF THE CORONARY ARTERIES

In addition to the anatomic dissection of the coronary arteries, their distribution and patency have been studied by use of injection mediums. As early as 1855, Hyrtl injected the coronary vessels with a metallic alloy of low-melting point. Subsequent corrosion of the heart muscle revealed the pattern of the coronary distribution.

van der Grint (1949) applied a similar technique, using a plastic material (Plexene). This method also sacrifices the heart muscle, and al-

terations in the vessels cannot be correlated with myocardial lesions. One may visualize the distribution of the coronaries and locate alterations in them by injection of the arteries with radiopaque material and subsequent roentgenography of the heart.

Gross (1921) devised a technique for injecting the coronary arteries with barium sulfate suspension in gelatin under pressure, by employing a standardizing and calibrating device. This technique or modifications and extensions of it have

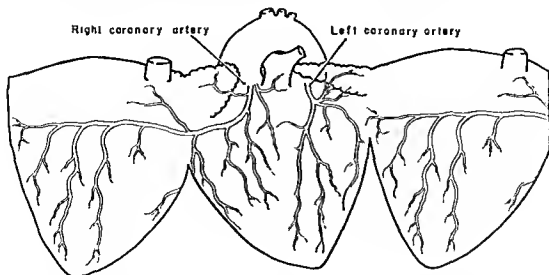


Figure XVIII-18. The distribution of the coronary arteries as found in 5-17 per cent of adult human hearts. (Adapted from Spalteholz.) The right coronary artery here predominates, the ramus marginis obtusi being the terminal branch of the left coronary artery.

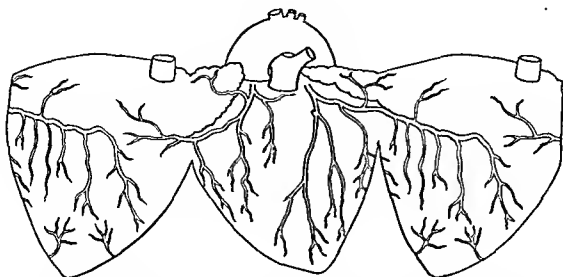


Figure XVIII-19. The distribution of the coronary arteries as found in about 10 per cent of adult human hearts. (Adapted from Spalteholz) The left coronary artery predominates, its final branch being the ramus ventriculi sinistri posterior (posterior descending artery).

been widely employed with varying results and for specific purposes.

In order to obtain an estimate of the capacity of the coronary arteries during life in hypertensive and ischemic hearts, Harrison and Wood (1949) injected the arteries with radiopaque gelatin at the known diastolic pressure of the patient. Because their skiagrams did not distinguish whether points of narrowing represented sites of atheroma or of canalized thrombi and because it was repeatedly noted that at sites of actual narrowing the skiagram might reveal no abnormality, they carefully checked their radiographic findings anatomically and histologically (Figure XVIII-20).

Because the method of Gross did not reveal the distributions of minute or penetrating branches of the coronary vessels, Schlesinger (1938) and associates, after injection (of lead phosphate in agar), sectioned the heart in a manner designed to expose the remote ramifications of the coronary tree for radiography. Sections were so disposed that the conical heart muscle was unrolled to make all the vessels lie in the same flat plane. This made all vessels, regardless of their normal relationships, equally visible roentgenologically and was particularly valuable in demonstrating alterations in otherwise obscure twigs to the septum.

To insure penetration of small branches of the coronaries, Prinzmetal and associates (1942) used an injection medium with a viscosity approaching that of blood. They determined the quantitative collateral circulation by clamping

the coronary vessels alternately and measuring volumes of material injected.

To determine collateral circulation, various dyes have been employed in the injection medium with some success and with varied results. Several techniques for injection are briefly described below.

Gross (1921) originally injected the coronary arteries 48 hours postmortem, after rigor had subsided. However, this interval may be varied considerably, the injections performed within a few hours postmortem or after the hearts have been at ice-box temperature for several days. To overcome rigor, the heart is placed in saline solution at 37 C. for four hours. The injection is performed with the heart and all injection material at standard temperature.

Technique of Gross for Injection of Coronary Arteries. Cardiac chambers are washed free of blood clot. The loose tissue about the aorta is bluntly dissected free, to expose the coronary arteries at their sites of emergence. A cannula, with a snugly fitting flanged glass nozzle, is inserted into each coronary orifice. A silk thread is looped about the coronary artery close to its point of emergence from the aorta, the flanges of the cannula being below the loop which is tightened about the cannula. Rubber tubing is attached to the cannulae and connected by a Y-tube. The heart is suspended by inserting a glass rod under the bridge of the pericardium which lies between the great

vessels and the atria, and this rod is supported on a tripod.

To maintain standardized mechanical factors, Gross devised a double-decked or duplex incubating apparatus. The cannulated heart is suspended in the upper chamber on a tripod. The lower chamber contains the injection mass and saline solution, each in a sealed or capped container, maintained at standard temperatures by electric immersion heaters. A compressed air tank with pressure gauge or mercury manometer and outlet tube can be connected by conduits to inlets in either the saline solution or the injection mass, the contents of the container being forced through an outlet tube. Both outlet tubes extend to the upper chamber of the apparatus where they can alternately be attached to the coronary cannulae. The coronary arteries are washed clean with saline solution. Then the pressure tube is connected with the flask containing the injection mass. The mass is forced into the vessels until the mercury manometer reading remains constant at 150 mm. without additional pressure. The vessels are tied off, cannulae removed and the heart immersed in cold water. With a suction apparatus, the chambers of the heart are freed of any accumulated injection mass. The heart is then immersed in cold formalin until it is fixed and bleached, when it is ready for preparation of the stereoscopic roentgenogram.

To avoid objections that the stereoscopic roentgenogram of the heart does not give a clear precise picture of the specific vessel involved, or does not visualize the smaller twigs of the coronaries, Gross and Kugel (1933-34) modified this original technique by slicing the injected and fixed heart transversely into strips of equal thickness (7 mm.) and took roentgenograms of them so that direct comparison could be made of the vasculature within the wall of the right and left ventricles and the interventricular septum. Transverse sections were made from the atrioventricular sulcus one-third of the way down to the apex.

Schlesinger's Method. The heart is warmed in a bath of physiologic saline solution at 44° C. A thermometer is placed directly into the chamber of the left ventricle, which is the slowest to reach the desired temperature. The entire procedure is conducted in a saline bath kept at 44-45° C. Schlesinger cannulates the arteries and connects them individually by tubes to receptacles containing injection mass or saline solution. Each receptacle is con-

nected to a separate manometer and by means of a Y-tube, both to the same syringe which supplies pressure. Three-way stopcocks permit pressure (of the syringe) to force the injection mass through both coronaries simultaneously or through right and left alternately. Injections are continued until manometer readings remain constant at 150 mm. of mercury for five minutes. To insure flow through anastomotic channels, the pressure to the left coronary is reduced to 0 or lower, and that to the right artery is kept at 150 mm. for several minutes. The process is then reversed with pressure to the right coronary reduced and that to the left maintained at 150 mm. The cannulae are clamped with the pressure at 150 mm. and the heart is disconnected. The mass is set by cooling the heart in a bath of iced physiologic salt solution. The injection medium is colored with methyl blue and basic fuchsin (in saturated alcoholic solution) for the right coronary artery and the left coronary artery, respectively.

After injection of the heart, the injection mass is allowed to harden and then the heart is incised according to a prescribed technique in order to unfold the heart and permit small

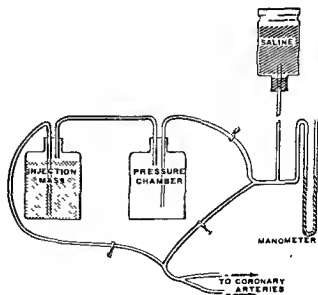


Figure XVIII-20. Diagram of Harrison and Wood's apparatus for injection of coronary arteries with radiopaque gelatin. (From Harrison, C. V. and Wood, P.: Hypertensive and ischaemic heart disease, a comparative clinical and pathological study, *Brit. Heart J.*, 11:205-229, 1949. Reproduced by permission of authors and publisher.)

TABLE XVIII-I

Normal Weights of Heart of Human Males and Females in Relation to Body Weight (Smith, 1928)

Body Weight				Weight of Heart							
Pounds		Kilo-grams		Minimum, Grams		Average, Grams		Maximum, Grams			
M	F	M	F	M	F	M	F	M	F		
105	90	47	40	165	135	205	162	241	193		
110	95	50	43	173	143	215	171	253	204		
115	100	52	45	181	150	225	180	264	215		
120	105	54	47	190	158	235	189	276	226		
125	110	56	50	198	165	245	198	287	237		
130	115	58	52	206	172	255	207	299	248		
135	120	60	54	213	180	265	215	310	259		
140	125	63	56	221	188	274	225	322	268		
145	130	65	58	229	195	284	234	333	277		
150	135	68	60	237	203	294	244	345	286		
155	140	70	63	245	211	304	253	356	295		
160	145	72	65	253	219	313	262	368	304		
165	150	74	68	261	225	323	272	379	313		
170	155	77	70	268	233	333	282	371	322		
175	160	79	72	280	240	343	288	372	330		
180	165	81	74	288	247	353	297	373	337		
185	170	83	77	296	255	363	306	382	343		
190	175	86	79	304	263	373	315	392	350		
195	180	88	81	312	271	382	324	402	356		
200	185	90	83	320	279	392	333	412	361		
	190		86		317		342		366		
	195		88		325		351		371		

vessels, regardless of their situation *in vivo*, to be visualized roentgenographically.

Prinzmetal's Method. Prinzmetal and co-workers (1942) attempted to demonstrate the distribution of the coronary system by the injection of a "more physiologic" medium, having a viscosity similar to that of blood and consisting of a mixture of lead carbonate, mercuric sulfide and gelatin with a viscosity of 5.40 as compared with 4.07 for blood. Prinzmetal and associates (1947) used radioactive erythrocytes which were found to penetrate the smallest branches of the coronary system. Human red cells were made radioactive by incubation with radioactive phosphorus in the form of Na_2HPO_4 . The radioactive erythrocytes in saline solution were perfused at a constant pressure of 100 mm. Hg, until the perfusate was seen to issue from the coronary sinus. The total amount of fluid perfused through the heart in each experiment was from 30 to 60 ml. and the time required was 30 to 60 seconds. The heart was then unrolled according to the method of Schlesinger. The distribution of the radioactive erythrocytes was determined by a Geiger counter at arbi-

trarily chosen sites on the endocardial and pericardial surfaces of the heart. By exposing the heart to x-ray films for from 15 to 48 hours, a radioautograph was obtained.

In another method, Prinzmetal injected into one coronary artery glass spheres of diameters ranging from 10 to 400 micra. These were suspended in a radiopaque mixture. Glass spheres injected into one coronary artery were recovered from the opposite coronary, the ventricular cavities and the coronary sinuses. The diameters of the various anastomotic channels were thus determined by the size of the spheres recovered. Salans and Tweed (1947) described a rapid technique using Neoprene, a synthetic latex. Each coronary was washed separately with saline solution. Barium sulfate in aqueous ammoniated solution of latex rubber was employed because it provides maximum radiopacity and because with it one

TABLE XVIII-2

Weight of Heart in 926 Persons without Clinical or Pathologic Evidence of Heart Disease, According to Body Length and Sex (Zeeb, 1942)

Body Length, Cm.	Heart Weight, Gm.		Body Length, Cm.	Heart Weight, Gm.	
	Males	Females		Males	Females
	$\bar{x} \pm s$	$\bar{x} \pm s$		$\bar{x} \pm s$	$\bar{x} \pm s$
135	254	219	168	317	277
136	256	220	169	319	279
137	258	222	170	321	281
138	260	224	171	323	283
139	262	226	172	325	284
140	264	227	173	327	286
141	266	229	174	329	288
142	268	231	175	330	290
143	270	233	176	332	291
144	272	235	177	334	293
145	273	236	178	336	295
146	275	238	179	338	297
147	277	240	180	340	299
148	279	242	181	342	300
149	281	243	182	344	302
150	283	245	183	346	304
151	285	247	184	348	306
152	287	249	185	349	307
153	289	251	186	351	309
154	291	252	187	353	311
155	292	254	188	355	313
156	294	256	189	357	315
157	296	258	190	359	316
158	298	259	191	361	318
159	300	261	192	363	320
160	302	263	193	365	322
161	304	265	194	367	323
162	306	267	195	368	325
163	308	268	196	370	327
164	310	270	197	372	329
165	311	272	198	374	331
166	313	274	199	376	332
167	315	275	200	378	334

s = standard deviation.

TABLE XVIII-3
Weight of Heart in Males
(Roessle and Roulet, 1932)

Age	Mean Heart Weight in Grams	Mean Body Weight in Kilograms	Number of Cases
Birth	23.37	3.373	60
Birth-6 months	28.20	3.430	15
7-12 months	38.8	4.47	5
1 year	58.93	12.360	6
2 years	64.125	12.147	4
3 years	74.58	15.300	6
4 years	83.71	18.433	7
5 years	98.00	17.375	3
6 years	104.00	—	1
7 years	119.00	20.400	4
8 years	113.5	—	2
9 years	116.00	20.800	1
10 years	185.00	31.000	1
11 years	140.00	27.000	1
12 years	160.1	37.600	4
13 years	198.00	37.850	2
14 years	—	—	—
15 years	241.75	44.900	8
16 years	252.70	43.812	7
17 years	279.00	49.340	7
18 years	217.25	42.400	4
19 years	285.00	55.990	20
20 years	282.07	51.998	13
21-25 years	305.48	55.125	90
26-30 years	312.02	51.617	69
31-35 years	314.29	55.714	74
36-40 years	312.19	54.635	61
41-45 years	317.23	57.255	51
46-50 years	335.64	56.400	28
51-55 years	346.81	58.800	16
56-60 years	333.57	54.066	21
61-65 years	324.42	53.380	14
66-70 years	359.33	59.400	9
71-75 years	308.33	45.430	6
76-80 years	318.00	47.400	2
85-90 years	321.00	43.450	2

may consistently obtain injection of precapillary arterioles that have a diameter of 15 to 75 micra. The medium is prepared with red and blue organic dyes for left and right coronaries, respectively. During injection, the heart is suspended for 5 to 15 minutes in a solution of 2 per cent glacial acetic acid and 4 per cent formaldehyde in 70 per cent ethyl alcohol. The heart is then fixed *in vacuo* at low temperature for 20 minutes, after which time it is cut according to the method of Schlesinger. This technique eliminates the use of an unstable injection medium, such as lead phosphate agar of Schlesinger which does not penetrate the small vessels consistently, and the prolonged exposure to a temperature of 44° C. It permits preparation of corrosive specimens as well as specimens suitable for dissection.

Durlacher's Method. A method of study of the coronary vessels and their contents

has been described by Durlacher and associates (1953). It provides an opportunity to visualize the entire vessel wall and its contents prior to sectioning and embedding, without the introduction of artefacts. In this method, the heart is removed in the usual fashion and drained of its contents. The proximal end of the ascending aorta is tied to a large cannula and normal saline solution is perfused under a pressure of 100 mm. of mercury. When the fluid escaping from the coronary sinus becomes clear, formalin is perfused through the cannula for 10 minutes. The heart is then suspended in formalin for several hours and later the coronary arteries and their major branches, together with an abundant layer of subepicardial tissue, are dissected from the

TABLE XVIII-4
Weight of Heart in Females
(Roessle and Roulet, 1932)

Age	Mean Heart Weight in Grams	Mean Body Weight in Kilograms	Number of Cases
Birth	21.4	3.198	44
Birth-6 months	21.37	3.396	8
7-12 months	36.33	5.18	3
1 year	53.66	9.262	6
2 years	54.21	11.166	7
3 years	65.8	12.450	5
4 years	71.75	—	4
5 years	90.8	18.000	5
6 years	82.16	—	3
7 years	94.5	—	2
8 years	109.00	19.200	2
9 years	115.00	23.800	3
10 years	118.00	26.000	1
11 years	135.00	29.500	1
12 years	166.00	—	2
13 years	170.00	—	2
14 years	201.00	42.2	2
15 years	201.33	36.700	3
16 years	204.5	50.225	4
17 years	220.00	47.660	3
18 years	225.5	44.550	4
19 years	254.6	47.830	3
20 years	262.25	56.100	8
21-25 years	265.8	50.441	14
26-30 years	252.6	51.705	21
31-35 years	269.5	55.270	4
36-40 years	233.14	49.010	7
41-45 years	288.36	55.300	11
46-50 years	298.88	56.344	9
51-55 years	292.4	60.540	13
56-60 years	316.33	56.940	12
61-65 years	307.68	50.240	16
66-70 years	362.00	53.625	4
71-75 years	309.5	48.000	7
76-80 years	335.4	48.340	5
81-85 years	292.33	37.400	6
86-90 years	284.00	34.1	2
Over 90 years	239.00	28.950	2

heart. The heart may then be examined in the usual manner. The arteries are decalcified in 5 per cent nitric acid and then placed in a solution of weak lithium carbonate. Following dehydration by ethyl alcohol, the vessels are immersed in clearing agent until transparent. Gross examination of the vessels is made with the help of transmitted light. The vessels may be sectioned transversely and embedded by placing the cleared segments first into benzene and then into liquid paraffin.

WEIGHT AND MEASUREMENTS OF THE HEART

In measuring the heart, one must take into consideration the size of the chambers and the presence or absence of rigor mortis. The technique of opening the heart must not vary. Measurements of the thickness of the walls of the right and left ventricles must always be taken in similar locations and care must be taken not to include the thickness of the trabeculae and papillary muscles.

The old rule that normally the size of the heart corresponds to that of the closed fist of the patient is inaccurate and should be discarded. The weight of the normal heart in an adult is usually stated to be between 275 and 325 grams. Nauwerck (1921) gave the weight of the heart of a man as 300 grams and of a woman as 250 grams. Smith (1928) concluded that the average weight of the heart of the adult man is 295 grams, and the average weight of the heart of the adult woman is 250 grams. His study excluded those hearts in which the records disclosed conditions known or believed to affect the weight of the heart. Thus, his figures were obtained by rigid selection of 1000 hearts from 6000 that were available for the study. He concluded that there is a definite correlation between the weight of the heart and the weight of the body and established the ratio as 0.43 per cent for males, and 0.40 per cent for females. The ratio is slightly higher in thin persons and lower in obese persons. This coefficient is less accurate for body weights of less than 45 Kg. (100 pounds) and more than 94.5 Kg. (210 pounds). Table XVIII-1 lists weights of normal hearts, according to Smith.

Clearing of the vessels prior to sectioning allows examination of the entire vessel wall and contents and permits one to make the gross diagnosis of the coronary lesions.

While injection of radiopaque material into the coronary arteries permits study of occlusion of the smallest branches and demonstration of anastomosing twigs, the method does not provide a better means of study of the coronary arteries than a careful and diligent dissection.

Zeek (1942) reported a statistical analysis of the weights of hearts from 926 adult bodies in which no clinical or pathologic evidence of heart disease or of any commonly recognized cause of myocardial hypertrophy was found. Her study revealed the following factors to have an effect on the weight of the heart: body weight, sex, body length and state of body nourishment. No effect of age or race on heart weight was demonstrated. Table XVIII-2 is taken from her study.

Roessle and Roulet (1932) gave tables of weights of the hearts in males and females (Tables XVIII-3 and XVIII-4) and weights of various parts of the heart (Table XVIII-5).

Coppoletta and Wolbach (1933) gave the weights of hearts of infants and children (Table XVIII-6).

Measurements of Valve. The figures that are usually given as the average of the normal valvular orifices of the adult heart, namely, aortic, 7-8 cm.; mitral, 9-11 cm.; pulmonic, 8-8.5 cm.; and tricuspid, 11-13 cm., are approximately correct. It is stated that measurement of the orifices by insertion of fingers or of a graduated wooden cone does not take into account the tonus or elasticity of the muscle (see Nomenclature and Criteria for Diagnosis of Diseases of the Heart, 1939).

Kopsch (1914) quoted Bizot, Wulff, Peacock, and Bouilland, and gave the circumferences of the various valves as shown in Table XVIII-7.

Kaufmann (1922) gave the measurements of the orifice of the mitral valve as 10 cm., of the aortic orifice as 7 cm., of the pulmonic as 8 cm.,

TABLE XVIII-5
Weight of Various Parts of the Heart
(Roessle and Roulet, 1932)

Age	No of Cases	Body Weight in Kilograms	Weight in Grams						
			Gross Heart	Left Ventricle	Right Ventricle	Inter-ventricular Septum	Left Atrium	Right Atrium	Interatrial Septum
MALES									
6-10 years	2	22.5	123.00	38.5	22.5	22.75	—	—	—
11-14 years	3	32.26	166.6	54.3	27.8	37.6	8.5	10.00	11.00
15-20 years	14	53.73	264.3	83.2	45.5	60.2	19.00	13.00	13.00
21-30 years	24	56.35	303.3	91.8	50.8	68.3	—	—	—
31-40 years	23	54.7	297.2	85.5	49.7	63.6	17.00	12.5	9.5
41-50 years	6	53.82	317.8	86.75	48.5	64.6	17.5	23.00	18.00
FEMALES									
1-5 years	1	14.00	50.00	18.00	10.00	11.00	—	—	—
15-20 years	4	51.25	255.5	79.75	41.12	55.75	11.00	12.5	12.5
21-30 years	2	58.00	227.00	68.5	41.5	47.00	17.00	13.00	9.00
31-40 years	2	49.5	328.00	84.00	48.00	61.5	—	—	—
41-50 years	1	55.00	376.00	105.00	52.00	68.00	—	—	—

TABLE XVIII-6
Weights of Hearts of Infants and Children
(Coppoletta and Wolbach, 1933)

Age	Body Length	Heart Weight
	Cm.	Gm.
Birth to 3 days	49	17
3 to 7 days	49	18
1 to 3 weeks	52	19
3 to 5 weeks	52	20
5 to 7 weeks	53	21
7 to 9 weeks	55	23
9 to 3 months	56	23
4 months	59	27
5 months	61	29
6 months	62	31
7 months	65	34
8 months	65	37
9 months	67	37
10 months	69	39
11 months	70	40
12 months	73	44
14 months	74	45
16 months	77	48
18 months	78	52
20 months	79	56
22 months	82	56
24 months	84	56
3 years	88	59
4 years	99	73
5 years	106	85
6 years	109	94
7 years	113	100
8 years	119	110
9 years	125	115
10 years	130	116
11 years	135	122
12 years	139	124

TABLE XVIII-7
Circumference of Valves, in Millimeters
(Kopsch, 1914)

Valve	Bisot		Wulff		Peacock		Bonilland	
	Male	Female	Male	Female	Male	Female	Max.	Min.
Tricuspid	123.6	107.5	129.7	124.5	115.3	101.6	108.4	106.1
Mitral	110.4	92.7	117.2	113.8	97.4	91.0	104.5	88.0
Pulmonic	71.8	66.9	—	—	84.7	82.5	76.7	67.7
Aortic	70.4	64.1	—	—	76.2	72.0	72.2	63.2

TABLE XVIII-8
Size of Pulmonary Trunk and Valve in Children,
According to Age (Hurwitz, 1947)

Age	No of Cases	Body Length (Cm.)			Weight of Heart (Gm.)			Circumference of Pulmonary Trunk (Mm.)			Average Diameter of Pulmonary Valve (Mm.)
		Small-est	Larg-est	Aver-age	Small-est	Larg-est	Aver-age	Small-est	Larg-est	Average S.D.*	
Prematures	251	28	48.5	43	3	36	13	10	30	19.5±5.4	6.3±1.8
N B.-3 mos.	222	49	64	52	6	50	19	15	42	24.7±3.1	7.9±1.0
3-6 mos.	97	50	68	59	12	94	29	18	48	28.7±3.7	9.2±1.2
6-9 mos.	67	51	113	65	20	74	36	20	48	31.2±4.9	10.1±1.6
9-12 mos.	44	50	78	68	25	72	42	21	58	32.9±6.1	10.6±1.9
12-18 mos.	67	64	87	75	28	84	49	21	59	34.9±4.1	11.2±1.3
18-24 mos.	34	58	91	81	36	105	61	25	52	36.4±4.5	11.7±1.3
2-3 yrs.	51	70	103	88	35	176	66	32	65	41.2±6.6	13.3±2.1
3-4 yrs.	30	66	113	93	50	130	77	33	65	41.3±5.9	13.3±1.9
4-5 yrs.	23	93	118	105	19	185	91	35	58	43.1±5.7	13.9±1.8
5-6 yrs.	33	83	126	107	48	178	99	30	80	44.8±6.1	14.4±1.9
6-7 yrs.	12	112	131	119	86	202	112	35	50	44.2	14.3
7-8 yrs.	14	109	134	128	75	156	113	44	70	50.0	16.1
8-9 yrs.	13	110	138	127	100	206	155	40	60	52.5	16.9
9-10 yrs.	13	97	151	130	82	280	150	40	70	53.5	16.7
10-11 yrs.	9	122	143	127	116	345	174	40	62	53.6	16.9
11-12 yrs.	10	103	145	138	105	356	191	40	70	54.1	17.5
12-13 yrs.	5	143	162	151	178	286	224	45	69	56.0	18.1
13-14 yrs.	1			168			597			70.0	21.9
14-15 yrs.	1			165			272			62.0	20.0
15-16 yrs.	2	120	160	140			240	45	70	57.5	18.6

* These figures represent the standard deviation of the distribution. Approximately 68 per cent of the cases will fall within a range included by the average \pm once the standard deviation, and 95 per cent within a range included by the average \pm twice the standard deviation. The number of cases in the age groups above six years is too small for this type of analysis.

TABLE XVIII-9

Thickness of Walls of Heart and Circumference of Valves (Saphir, 1951)

<i>Thickness* of Wall of Chambers, Mm.</i>	
Right and left atria	1-2
Left ventricle	8-10
Right ventricle	2-3
<i>Circumference of Valves, Cm.</i>	
Mitral	10
Aortic	7 5
Pulmonic	8 5
Tricuspid	12

* Note: In measuring the thickness of the ventricles, care must be taken not to include the thickness of the papillary muscles and columnae carneae.

and of the tricuspid as 12 cm. Hurwitt (1947) studied the size of the pulmonic valve of children. His results are given in Table XVIII-8.

Kaufmann stated that, in measuring the thickness of the heart, it is important to indicate the exact site that is measured. The pericardial fat tissue and the trabecular muscels should not be included in the measurements. He gave the thickness of the right ventricle as 0.5 to 0.7 cm., and that of the left ventricle as 1.1 to 1.4 cm. His measurements of the wall of the right ventricle are obviously too large, its average thickness probably being only 2 to 3 mm.

For practical purposes, it may be well to list the measurements given by Saphir (1951). Although they are average measurements, they will suffice in most instances (Table XVIII-9).

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Histochemical Procedures in The Study of Heart Disease

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HISTOCHEMICAL METHODS useful in the study of the heart are numerous and new methods are constantly being introduced. For this reason it has been necessary to restrict arbitrarily the techniques to be described. Selected for description are those which have been tried and found easy, reliable, and possible to perform without major dislocation of the usual procedures in the pathologic laboratory. We have found in our department that these techniques can be fitted into the routine of an autopsy service by selection of the cases to be studied.

General Principles. Certain general principles are to be kept in mind in doing histochemical procedures. The first applies to all autopsy studies: Only one chance, this one, is presented for the study of the case. If the appropriate fixation and handling of tissue are not done at the time of autopsy, the opportunity is lost forever. The second general principle is that histochemical procedures supplement rather than replace histologic procedures. Certain histochemical procedures, such as the Alcian Blue-PAS (Mowry)

or the Sudan Black B fat stain, give admirable over-all appearances in tissue sections. However, to practice good histochemistry one must do good histology and the beginner would be well advised to make familiar stains (hematoxylin and eosin, Mallory or Masson trichrome, Verhoeff or orcein van Gieson) on sections corresponding to his histochemical preparations, for purposes of orientation. Finally, these histochemical procedures are chemical methods of no greater or less chemical complexity than those carried out in most hospital clinical laboratories. They require the same chemical standards of laboratory procedures; they do not demand, for their performance, any particular talent not found in a good medical technologist.

General Directions. The following simple instructions include all that needs to be done for any histochemical procedure described.

1. Cut blocks of tissue 2 cm. by 3 cm. and not more than 5 mm. in thickness.
2. Place blocks in ice-cold buffered 10 per cent formalin and leave in refrigerator overnight. However, tissues that are to be tested

for the presence of any of the following substances should be placed in the designated fluid:

- Ribonucleic acid. Carnoy's fixative
- Sulphydryl (-SH) groups 1 per cent trichloroacetic acid in 80% alcohol
- Cholinesterase. saline, kept in deep-freeze cabinet
- Dehydrogenase. saline, kept in deep-freeze cabinet
- Glycogen absolute alcohol

Keep all fixing solutions ice-cold before, during, and after fixation.

3. Cut frozen sections 12-15 microns in thickness on all except paraffin-embedded tissues which are to be treated with periodic acid-Schiff's reagent (PAS) or tested for ribonucleic acid (RNA). For cholinesterase and succinate dehydrogenase, the sections should be 25-50 microns thick. Place the frozen sections directly into the reacting solution or substrate as they are cut. In addition, prepare ordinary paraffin sections.

4. Replace the tissue blocks in the fixative

and refrigerate, in case more sections are needed later.

5. Incubate the tissue sections and complete the techniques as outlined. (The use of small paper cups will facilitate carrying the sections through the solutions.) When the sections reach water just before the final dehydrating series, lift them up on to slides (which may be smeared with albumen) to smooth them out, dehydrate if desired, and mount.

6. Run controls simultaneously with the sections, using the same solutions before and after the control step. This step is usually incorporated in the incubating portion of the procedure. Consult outline of particular method for details, as there may be some variation in treatment of control, according to the procedure that is being run.

7. Be sure that all slides are labeled with autopsy number, name of procedure, and tissue being treated.

8. In general, have prepared solutions ready for use. Each procedure outlined sets forth instructions for making mixtures from previously prepared stock solutions.

METHODS

Periodic Acid-Schiff (PAS)

Principle. Most if not all carbohydrates of tissue, except for the nucleic acids, are made up of repeating glycol (HC-OH) groups (McManus, 1948). If two of these groups are adjacent (in so-called 1,2 glycols), periodic acid acts upon them to oxidize the hydroxyl group to aldehyde. The aldehyde is then colored with Schiff's reagent.

Fixative. Any fixative may be used, but in testing for glycogen, absolute or 95 per cent alcohol is recommended.

Method.

Preparation of Schiff's reagent.

1. Weigh out 1 Gm. basic fuchsin.
2. Weigh out 1 Gm. sodium metabisulfite.
3. Boil 200 ml. distilled water.
4. Add fuchsin and stir.
5. Cool to 65° C.

6. Filter and keep at 65° C. throughout filtration.

7. Add 20 ml. N HCl (86.3 ml. HCl, sp. gr. 1.16, made to 1000 ml. with distilled water).

8. Cool to 25° C.

9. Add sodium metabisulfite.

Keep in dark. The fluid takes about 24 hours to become orange or straw-colored; then add 1 Gm. activated charcoal, mix well and filter. Filtrate should be clear. It is then ready for use.

Sulfurous acid rinsing solution (for 3 Penn-field dishes).

- 10% sodium metabisulfite. 36 ml.
- 1 N hydrochloric acid. 36 ml.
- Distilled water 528 ml.

A. For paraffin sections:

1. Take paraffin sections to water.
2. Wash in running tap water.

3. Treat with 0.5 per cent periodic acid in water, 5 minutes.
4. Rinse in distilled water.
5. Place in Schiff's reagent, 15 minutes.
6. Rinse in three changes of sulfurous acid, each 2 minutes.
7. Wash in running water, 3 to 10 minutes.
8. Stain in Harris' hematoxylin, 20 to 30 seconds.
9. Wash in running water, 5 minutes.
10. Dehydrate in two changes of 95 per cent alcohol.

11. Pass through two changes of absolute alcohol.

12. Clear in xylene or toluene and mount in balsam or Permount.

(Note: Steps 8 and 9 are optional.)

Results. Tissue and cellular materials, containing carbohydrate, take a magenta to purple color. (See Figures XIX, 1-4.)

B. For frozen sections:

1. Place frozen sections in 0.5 per cent aqueous periodic acid, 5 minutes.

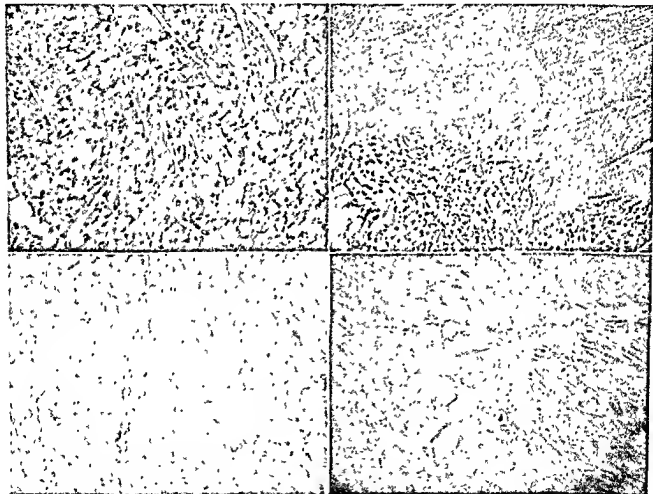


Figure XIX-1 (left upper). Glycogen in normal myocardium of dog, fixed in Rosman's fluid at room temperature. Periodic acid-Schiff. X 210.

Figure XIX-2 (right upper). Myocardium from dog killed 30 minutes after ligation of coronary artery. The ischemic area (top) is free of glycogen, while the surrounding myocardium (bottom) contains a normal amount. Periodic acid-Schiff. X 210.

Figure XIX-3 (left lower). Normal myocardium of dog after diastase digestion. The sarcoplasm is colorless while the sarcolemma continues to stain. Diastase-periodic acid-Schiff. X 210.

Figure XIX-4 (right lower). Ischemic myocardium 21 hours after ligation of the coronary artery. Diastase-periodic acid-Schiff. The ischemic area is PAS-positive after diastase digestion, and is sharply demarcated from the surrounding myocardium. X 210.

2. Wash in several changes of distilled water.
3. Place in Schiff's reagent, 10 minutes.
4. Rinse in three changes of sulfurous acid, each 2 minutes.
5. Wash in tap water.
6. Counterstain, if desired, with 20-30 ml. of Harris' hematoxylin.
7. Wash well in water.
8. Mount in glycerin or glycerin jelly, or dehydrate and mount in balsam.

Alcian Blue-PAS

Principle. Alcian Blue 8 G S is a patented, water-soluble tetraalkylthiuronium derivative of chloromethylated copper phthalocyanin (Venkataraman, 1952). This important commercial dye was introduced as an empirical stain for mucin by Steedman (1950). Alcian Blue (AB) behaves like a basic dye but is unusually stable and resistant to decoloration.

According to Dr. Robert W. Mowry of this department (personal communication), Steedman's method yields staining that is less intense and less selective than that obtained when a lower pH and a more dilute solution of dye are used. The improved AB solution yields strong coloration of most epithelial mucins, mast cell granules, connective tissue mucins, and certain microbial capsules. Comparison with other staining methods and the results of testing pure substances indicate that AB stains acidic carbohydrates (mucopolysaccharides). Reference is made to these studies by McManus in his chapter on Histochemistry of Connective Tissue in Asboe-Hansen's *Connective Tissue in Health and Disease* (1954). Our Alcian Blue methods and the results obtained with them have not been previously published in full form.

Method for Acidic Groups and 1,2 Glycols (of Carbohydrates).

1. Take sections to water. (Remove mercury deposits, if necessary, with Lugol's solution) and thiosulfate routine.
2. Stain in 0.1 per cent Alcian Blue in 3 per cent acetic acid, 30 minutes.
3. Wash in running tap water, 2 minutes. Rinse in distilled water.

4. Treat in 0.5 per cent periodic acid (HIO_4), 10 minutes.

5. Wash in running tap water, 5 minutes; rinse in distilled water.

6. Treat in Schiff's reagent, 10 minutes.

7. Rinse in three changes of sulfurous acid solution (see PAS technique), each 2 minutes.

8. Wash in running tap water, 5 minutes.

9. Stain in Weigert-Lillie's alum hematoxylin (equal parts of 4 per cent aqueous iron alum and 1 per cent alcoholic hematoxylin), 5 minutes. (This step may be omitted in special instances, if nuclear staining is not desired.)

10. Wash in running tap water, 2 minutes.

11. Dip in saturated aqueous picric acid, 1 minute. Rinse in tap water for a few seconds.

12. Dehydrate, clear and mount.

Results. Exclusively acid substances (various connective tissue mucins) are blue; neutral polysaccharides (glycogen, and mucus of Brunner's gland) are magenta; and certain substances (most epithelial mucins and cartilaginous ground substance) are colored by both AB and PAS, yielding varying shades of purple to very deep blue. The cell bodies of fungi are red to purple while mucoid capsules (e.g., that of *Cryptococcus neoformans*) are blue. Other features appear about the same as seen with the ordinary PAS (or PASH, if hematoxylin is used).

Ritter and Oleson (Hale-PAS)

Principle. The principle underlying the Hale stain is not certain (Ritter and Oleson, 1950). The method stems from the observation that colloidal iron (ferrie) hydroxide is bound by tissue mucopolysaccharides and can be demonstrated by Perls' prussian blue method.

Method.

1. Zenker's solution or Bouin's fluid are preferred fixatives but formalin is also satisfactory.

a. Fix the fresh specimen in Zenker's solution for 24 hours and then wash in running tap water for 24 hours before immersion in 80 per cent alcohol for 24 hours, or

b. Fix in Bouin's fluid for 24 hours and then immerse in 80 per cent alcohol for 24 hours, or

c. Fix in 10 per cent formalin for 24 hours.

2. After fixation, place the specimen in 95 per cent alcohol for 24 hours, then in absolute alcohol for 4 to 10 hours, and subsequently leave in toluene overnight.

3. Place the specimen in paraffin at 50-60° C. for 4 hours and then embed in fresh paraffin.

4. Cut sections from 4 to 6 microns in thickness, mount on slides with glycerin-egg albumen and put in the oven at 65° C. for at least 1 hour.

5. Immerse the slides in xylene for 2 minutes to remove the paraffin and then pass through absolute alcohol and 95 per cent alcohol to tap water. If the specimen was fixed in Zenker's solution, place the slides next in strong iodine solution U.S.P. (Lugol's iodine) until nutmeg-brown, then leave in 5 per cent sodium thiosulfate until bleached, and wash well in running tap water.

6. Immerse the slides in a solution composed of equal parts, by volume, of dialyzed iron and glacial acetic acid for 2 minutes, and wash well in distilled water.

7. Place in a solution composed of equal parts of freshly prepared 0.02 M potassium ferrocyanide and 0.14 M hydrochloric acid for 10 minutes.

8. Wash the slides well with distilled water and treat by the periodic acid-Schiff reagent method, as follows:

a. Immerse in 0.5 per cent periodic acid, 5 minutes.

b. Wash in distilled water.

c. Immerse in Schiff's reagent, 15 minutes.

d. Rinse in three changes of sulfurous acid, each 2 minutes.

e. Wash in running tap water, 3 to 5 minutes.

f. Dehydrate in graded alcohols, clear in xylene, and mount in balsam.

Results. Acid groups, including carbohydrates, give a blue to green color; non-acid carbohydrates, magenta to purple. A section

carried through the procedure, omitting step 6, should be run as control. Preformed ferric iron colors green-blue in the control.

Toluidine Blue for Metachromasia*

Principle. Complex carbohydrates, containing either carboxyl or sulfuric acid groups or both, are metachromatic (stain red) with toluidine blue solutions. The given procedure colors both, but in order to produce maximal red color in predominantly carboxyl-containing carbohydrates, it is desirable to expose to air ("air-dry") after dehydration and before clearing in xylene.

Method.

1. Take paraffin sections to water.

2. Treat in 0.01 per cent aqueous toluidine blue, 30 minutes.

3. Wash briefly in water.

4. Dehydrate in 95 per cent and absolute alcohol.

5. Remove from alcohol and "dry" briefly in air until opaque.

6. Clear in several changes of xylene.

Results. Acid mucopolysaccharides are red to pink. If granules of mast cells are colored red, staining procedure is probably accurate.

Sudan IV

Principle. The Sudan dyes have a preferential solubility in fat as compared to alcohol. The section is carried into a concentrated solution of Sudan IV in alcohol-acetone and the dye diffuses into the fat. The solution of the dye is volatile and the dishes should be kept covered at all times to prevent precipitation of the dye on the section.

Method.

1. Frozen sections to water.

2. Dip for an instant in 70 per cent alcohol.

3. Stain in Hercheimer's Scarlet Red solution 2 to 5 minutes. (Formula: Scarlet red, 1 Gm.; alcohol, 70 per cent, 50 ml.; acetone, C.P., 50 ml.)

4. Wash quickly in 70 per cent alcohol.

* The technique and details are those of Dr. R. W. Mowry.

5. Wash in water.
6. Stain nuclei in alum hematoxylin, if desired.

7. Wash thoroughly in water.
 8. Mount in glycerin or glycerin jelly.
 Results. Nuclei are blue, fat, orange to red, cholesterol, less brilliantly red.

Sudan Black B

Principle. Sudan Black B works on the same principle of preferential solubility as the other Sudan dyes, but appears to have the added property of coloring some complex lipids and phospholipids. It will color lipids that are preserved in paraffin sections, including myelin sheaths, "ceroid" and "wear-and-tear" pigment (Gomori, 1939, Baker, 1944).

Method.

Preparation of Sudan Black B Solution

Saturate 70 per cent alcohol with Sudan Black B with repeated shakings. Leave overnight. Add more dye, shake repeatedly and again leave overnight. Filter before use.

Procedure.

1. Place frozen sections in saturated Sudan Black B in 70 per cent alcohol, 7 to 10 minutes.

2. Rinse in 70 per cent alcohol.

3. Counterstain if desired.

4. Mount in glycerin or glycerin jelly.

Results. Frozen sections, lipochromes, ceroid and simple and complex lipids are black, in paraffin sections, complex lipids and pigments are black.

Alkaline Phosphatase

Principle. Phosphate is split from the substrate sodium glycerophosphate by alkaline phosphatase in the tissue. It precipitates as calcium phosphate. Subsequent reactions replace this with cobalt sulfide, leaving black coloration at the sites of activity.

Method.

1. Fix overnight in cool, buffered formalin.
2. Cut frozen sections. Mount on slides smeared with albumen.
3. Place in distilled water, 2 minutes.

4. Incubate at 37° C. for 1 to 4 hours in following substrate:

3 per cent (± 1 M) solution Na glycerophosphate, 5-19 ml.

2 per cent (± 2 M) calcium chloride, 20-25 ml.

10 per cent (± 5 M) magnesium chloride, 10 drops

Sodium barbital powder, 0.5-1 Gm.

Distilled water, to make 50 ml.

Adjust pH to 9.1

(If mixture is turbid, filter before use.)

5. Wash under tap, 1 minute.

6. Immerse in 1-2 per cent solution of any soluble cobalt salt (e.g., acetate) for 5 minutes.

7. Wash under tap, 1-2 minutes.

8. Immerse in dilute solution of yellow ammonium sulfide (a few drops added to coplin jar of distilled water), 5 minutes.

9. Wash under tap.

10. Counterstain with eosin (0.5-1 per cent aqueous eosin), if desired.

11. Run up alcohols into xylol. Mount in Clarite or Permout if desired, or in glycerol or glycerin jelly.

Proceed as above but replace sodium glycerophosphate with distilled water in substrate.

Results. Sites of activity take a black color.

5-Nucleotidase

Principle. This procedure is carried out at pH 8.3 for optimal activity of 5-nucleotidase, since the method used is similar to that of alkaline phosphatase except for the substrate. The 5-nucleotidase in the tissue splits off PO_4 from adenylic acid, which precipitates as CaPO_4 . The calcium is then replaced with cobalt and the PO_4 is replaced by sulfide, leaving black cobalt sulfide at the sites of activity. (See Gomori, 1949; McManus and Lupton, 1953.)

Method.

1. Fix overnight in cool, buffered formalin.
2. Cut frozen sections and mount slides smeared with albumen.
3. Place in distilled water, 2 minutes.
4. Incubate at 2-6 hours at 37° C. in following mixture: Muscle adenylic acid 20 mg. in 20 ml. of 0.1 to 0.2 M barbital buffer at

pH 8.3. Add 20 ml. 2 per cent calcium chloride. Add few drops of 10 per cent magnesium chloride. Adjust final solution to pH 8.3.

5. Wash under tap, 1 minute.

6. Immerse in 1-2 per cent solution, of soluble cobalt salt (acetate, chloride, sulfate, or nitrate), 5 minutes.

7. Wash under tap, 1-2 minutes.

8. Immerse in dilute ammonium sulfide (several drops added to a jar of distilled water), 5 minutes.

9. Wash under tap, 3-4 minutes.

10. Counterstain as desired in 1 per cent aqueous eosin.

11. Run up alcohols into xylol. Mount in Clarite or Permount if desired, or in glycerol or glycerin jelly.

For control, carry out above steps but omit the muscle adenylic acid from the substrate.

Results. Sites of activity are black (Figure XIX-5).

Acid Phosphatase

Principle. In acid media only the acid phosphatase works to split off PO_4 from glycerophosphate in substrate. The phosphate combines with lead to precipitate. Ammonium sulfide displaces the phosphate to form colored lead sulfide. (See Gomori, 1941.)

Method.

1. Fix overnight in cold, buffered formalin.

2. Cut frozen sections; place on slides smeared with albumen.

3. Place in distilled water, 2 minutes.

4. Incubate at 37°C . for 1-24 hours (prostate 1-2 hours, others 6-8 hours) in following substrate: 0.05 veronal acetate buffer pH 5, 500 ml.; lead nitrate, 0.6 Gm.; 3 per cent (.1 M) Na glycerophosphate, 50 ml.; incubate 37°C . for 24 hours; filter. Keep refrigerated. (Add 5 per cent of volume of distilled water; discard if turbid.)

5. Rinse in distilled water.

6. Place in 1-2 per cent acetic acid, 1-2 minutes.

7. Rinse in distilled water.

8. Immerse in dilute ammonium sulfide about 3 minutes.

9. Wash under tap, 4 minutes.

10. Counterstain as desired.

11. Run up alcohols if desired and carry out steps 12 and 13.

12. Clear in gasoline or tetrachloroethylene (not xylol).

13. Mount in Clarite dissolved in same solvent (gasoline or tetrachloroethylene) or mount from water in glycerol or glycerin jelly.

For control, carry out above steps but omit the Na glycerophosphate from the incubation mixture, replacing it with 50 ml. distilled water.

Veronal acetate buffer is prepared as follows:

Sodium acetate	9.7 Gm.
Sodium diethyl barbiturate....	14.7 Gm.

Place in a 500-ml. volumetric flask, mix well and slowly add distilled water, swirling after each addition, to a volume of 500 ml. solution. This is the veronal-acetate of Michaelis' stock solution. It should be kept at 4°C .

Working solution for acid phosphatase, pH5:

0.1 N HCl	9 ml. or 180 ml.
Stock of veronal acetate	5 ml. or 100 ml.
Distilled water	11 ml. or 220 ml.
Total	25 ml. or 500 ml.

Incubate for 24 hours at 37°C .

It is not re-usable and should be kept at 4°C .

Results. Sites of activity appear dark brown-black.

Peroxidase

Principle. An excess of hydrogen peroxide (H_2O_2) is added to the tissue containing peroxidase. This enzyme transfers the oxygen from H_2O_2 to the benzidine, oxidizing it and rendering it colored (Adler and Adler, 1904; Goodpasture, 1919; LePehue, 1919; Washburn, 1928; Osgood, 1937).

Stock Solution. Benzidine solution 0.2-3 per cent in 95 per cent alcohol. To each 100 ml. of solution add about 0.5 Gm. Na nitroprusside dissolved in a few milliliters of water. If refrigerated, it will keep for months.

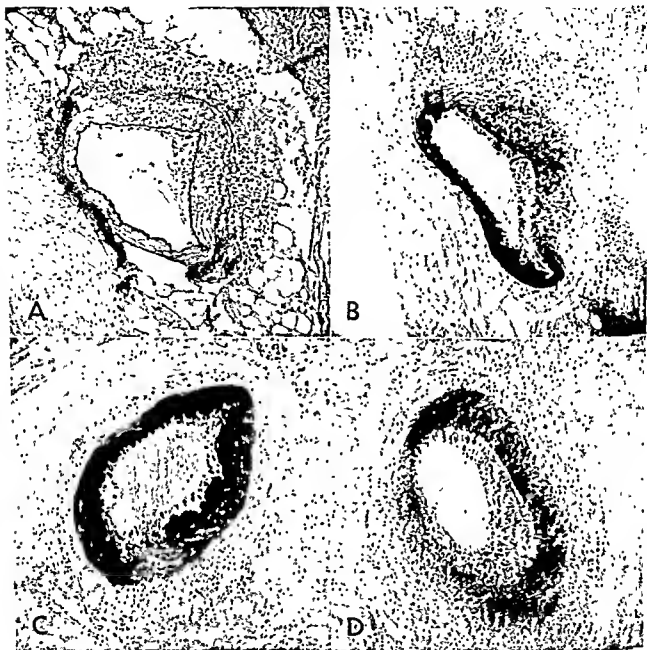


Figure XIX-5 Necrotizing arteritis studied by 5-nucleotidase method (McManus, Gilmer and Torbert, unpublished). A, Green-van Gieson stain; B, C and D, 5-nucleotidase, histochemical method. In the 5-nucleotidase preparations, the sites of enzyme activity appear black. A and B, paired sections showing destruction of wall of coronary artery on the right side, C, slight regional involvement by necrotizing arteritis; D, extensive destruction of vessel wall (necrotizing arteritis).

Method.

1. Fix overnight in cool, buffered formalin.
2. Cut frozen sections; mount on slides smeared with albumen.
3. Place in distilled water, 2 minutes. (It may be preferable to carry sections directly into substrate.)
4. Mix equal volumes of stock solution and a 1:5 dilution (for hemoglobin) or a 1:50 di-

lution (for myeloid granules) of commercial (3 per cent) hydrogen peroxide. Pour over slide and leave for 5 minutes.

5. Decant; wash briefly in water.
6. Counterstain with a red nuclear stain (0.5 per cent aqueous acid fuchsin).
7. Mount directly in glycerol or glycerin jelly, or run up through alcohols into xylol and mount in Clarite or Permount.

Results. At sites of activity, myeloid gran-

ules are intensely dark blue, and hemoglobin is dark brown to blue.

Dehydrogenase

Principle. The tissue dehydrogenase splits off hydrogen from added substrates (succinate, lactate, etc.). The tetrazonium dyes accept the hydrogen split off (similar to coenzyme diphosphopyridinenucleotide) and become colored compounds when reduced (Zweifel, Black and Shorr, 1950, Seligman and Rutenburg, 1951).

Method.

Phosphate buffer stock solutions

Solution No. 1

$\text{Na}_2\text{HPO}_4 \cdot \text{H}_2\text{O}$ 13.8 Gm
Distilled water 1000 ml.

Solution No. 2

$\text{NaH}_2\text{PO}_4 \cdot 7 \text{H}_2\text{O}$ 26.81 Gm.
Distilled water 1000 ml.

Both are 0.1 M solutions and should be kept refrigerated.

Working solution at pH 7.5

Solution No. 1 43 ml. or multiple
Solution No. 2 7 ml. or multiple

Adjust final pH in pH-meter by adding drop by drop of solution needed. Solution No. 1 elevates pH, whereas No. 2 lowers it.

Procedure.

1. Cut fresh frozen sections 25-50 microns thick.

2. Incubate tissue slices for 45 minutes at 37° C. in following substrate:

Distilled water 1 part
Phosphate buffer, 0.1 M, pH 7.5 . . . 1 part
Necotetrazolium, 0.1 per cent 1 part
Sodium succinate, 0.1 M 1 part

Preheat substrate to 37° C. before placing sections in it. See that sections lie flat.

3. Wash briefly in distilled water.

4. Mount in glycerogel.

For control, proceed as above, omitting sodium succinate from the substrate.

Results. Sites of activity appear purple-red.

Nonspecific Esterase

Principle. The esterase splits the acetate from *a*-naphthyl acetate, leaving an *a*-naphthyl compound which is coupled to diazo Blue B to form a colored azo dye at sites of activity (Nachlas and Seligman, 1949 a, b; Gomori, 1950).

Method.

1. Fix overnight in cool, buffered formalin.
2. Cut frozen sections. Mount on slides smeared with albumen.

3. Place in distilled water, 1 to 2 minutes.

4. Incubate at room temperature in following mixture, 5-15 minutes:

a-Naphthyl acetate, 40 mg. in 0.5 ml. acetone

Add 40 ml. .1 M phosphate buffer, pH 7.4

Agitate until initial cloudiness disappears
Add 40 mg. diazo Blue B (Dajac Laboratories)

Filter

5. Wash in distilled water.

6. Mount in glycerogel.

For control, carry out above steps but incubate in solution containing distilled water instead of *a*-naphthyl acetate.

Results. Sites of activity are blue.

Distribution. Bronchial epithelium, elastic layer of large blood vessels, liver, homogeneously stained pancreatic acini, convoluted tubules in cortex of kidney, Auerbach's plexus, cardiac portion of stomach.

Cholinesterase

Principle. The substrate acetylthiocholine is attacked by tissue cholinesterase, liberating free thiocholine which then precipitates as its cupric salt. The ammonium sulfide displaces the thiocholine moiety leaving dark brown cupric sulfide (Koelle and Friedenwald, 1949).

Method.

Stock solution.

Copper sulfate

$(\text{CuSO}_4 \cdot 5 \text{H}_2\text{O})$ 0.3 Gm.

Glycine 0.375 Gm.
 Magnesium chloride
 ($\text{MgCl}_2 \cdot 6 \text{H}_2\text{O}$) 1.0 Gm.
 Maleic acid 1.75 Gm.
 N(4 per cent) NaOH 30 ml.
 Hot saturated (about 40 per cent)
 Na_2SO_4 170 ml.

Procedure.

1. Cut fresh frozen sections.
2. Mount on slides smeared with albumen.
3. Control. Place in 0.000001 M di-isopropyl-fluorophosphate (DIFP) for 30 minutes prior to incubation.
4. Incubate for 10-60 minutes at 37° C. in acetylthiocholine iodine, 20 mg, in a few drops of water. Add 10 ml. of stock solution.
5. Rinse in two or three changes of saturated Na_2SO_4 .
6. Immerse in dilute ammonium sulfide (several drops added to a jar of water).
7. Counterstain as desired.
8. Run up through alcohol and into xylol.
9. Mount in Clarite or Permount.

Results. Sites of activity appear dark brown

Cholinesterase 2

Principle. Carbonell (1956) has shown that the conducting system of the human heart has an esterase which splits a pentadecanoyl choline in the presence of cobalt to form an insoluble compound that can be blackened by ammonium sulfide.

Method.

Stock solutions.

Pentadecanoyl choline, 0.02 M \pm 7 per cent solution.

Cobalt acetate, 0.0125 M, in maleate buffer, 0.03 M, pH 7.6-7.8.

Procedure.

1. Incubate frozen sections, 5-6 hours, in mixture of cobalt acetate stock solution, 50 ml., and pentadecanoyl choline solution, 1 ml.
2. Wash sections in distilled water.
3. Place sections in 1 per cent yellow am-

monium sulfide in 70 per cent alcohol, 2 minutes.

4. Wash in water, dehydrate if desired, and mount in glycerin or glycerin jelly.

Results. Bundle and branches are black.

Desoxyribose Nucleic Acid (DNA)- Feulgen

Principle. The hydrochloric acid hydrolyzes desoxyribose (nuclear nucleic acid) to form free aldehyde groups in the tissues. These are subsequently colored magenta to purple by Schiff's reagent.

Method.

1. Bring sections to water and remove mercury if necessary.

2. Rinse briefly in cold N HCl. (This step is not absolutely necessary.)

3. Place in N HCl at 60° C., 10 minutes exactly.

4. Rinse briefly in cold N HCl and then in distilled water. (This step is not necessary.)

5. Transfer to Schiff's reagent, 10 minutes.

6. Drain and rinse in three changes of freshly prepared bisulphite solution (5 ml. 10 per cent $\text{K}_2\text{S}_2\text{O}_5$; 5 ml. N HCl; water to 100 ml.).

7. Rinse in warm tap water or preferably in water at 42° C.

8. Counterstain if desired (1 per cent aqueous light green, 1 minute, or 0.5 per cent alcoholic Fast Green, $\frac{1}{2}$ to 1 minute).

9. Dehydrate in alcohol.

10. Clear in xylene and mount in balsam.

Results. DNA appears in shades of red-purple.

Ribonucleic Acid (RNA)-Methyl Green- Pyronine

Principle. This is a straightforward direct staining method like other routine dyes. No essential sequence of chemical reactions is involved, although Kurnick (1955) appears to find considerable specificity for RNA coloring.

Method.

Preparation of stain. Dissolve 0.5 Gm. purified methyl green and 0.1 Gm. pyronine Y in 100 ml. hot distilled water. Cool. Store in amber bottle. It will keep about 3 or 4 months.

Procedure.

1. Fix in cold Carnoy's solution, 3 to 4 hours.
 2. Place in absolute ethanol, two changes, each 1 hour.
 3. Place in cedarwood oil until section sinks, 1-2 hours.
 4. Immerse in toluol, 3 to 5 minutes.
 5. Infiltrate with paraffin, 3 changes (Watterman's mixture, Turtox), 49-51° C., each 1 hour.
 6. Block in mold.
 7. Cut sections and mount on slides smeared with albumen or with help of warming plate at 37-38° C. until sections stick to slide. (May need to add several drops distilled water.)
 8. Place in xylol, 1 minute.
 9. Run through absolute, 95 per cent, 70 per cent, and 50 per cent alcohols to water.
 10. Stain in methyl green-pyronine, 1 minute.
 11. Rinse several times in distilled water. Blot briefly with bibulous paper.
 12. Immerse in mixture of 3 parts tertiary butyl alcohol and 1 part absolute alcohol, 5 minutes.
 13. Clear in xylol for two 5-minute changes.
 14. Wipe off excess xylol.
 15. Mount in Clarite or Permount.
- Run through steps 1-9 in above procedure. Then place glass ring around section held in place with vaseline. Fill space over the section with ribonuclease solution. Incubate in oven at 37° C. for 1 hour. Do likewise with another slide, using distilled water instead of ribonuclease. After incubation, carry both test and control slides through steps 10-15.

Methyl green is purified by extracting several times with chloroform in vacuum filter

apparatus. The purified methyl green will be left in the filter paper.

Results. Sites of RNA show as red color.

Sulphydryl (-SH) Groups

Principle. The reagent, 2,2'-dihydroxy-6,6'-dinaphthyl disulfide, when used in excess at pH 8.5, reacts with the active, protein-bound or fixed sulphydryl groups to form a colorless substance which can be converted into an azo dye by coupling with tetrazotized orthodiamidine (Dajac's Diazo Blue) (Barnett and Seligman, 1952).

Method.

1. Fix in 1 per cent (TCA) trichloroacetic acid in 80 per cent ethanol in cold, overnight.
2. Pass through several changes of 95 per cent ethanol, each 1 hour.
3. Pass through two changes absolute ethanol, each 1 hour.
4. Clear in cedarwood oil until section sinks.
5. Immerse in toluol, 5 minutes.
6. Infiltrate with paraffin 3 changes, each 1 hour.
7. Embed in paraffin; cut; mount.
8. Immerse in xylol, 2 minutes.
9. Run through alcohols to water.
10. Incubate 1 hour at 50° C. in mixture of 35 ml. 0.1 M Michaelis' barbital buffer, pH 8.5, and 15 ml. absolute ethanol containing 25 mg. 2,2'-dihydroxy-6,6'-dinaphthyl disulfide.
11. Cool 10 minutes at room temperature.
12. Rinse briefly in distilled water.
13. Wash in two changes distilled water acidified to pH 4 to 4.5 with acetic acid (1 drop glacial acetic acid to 200 ml. water), 10 minutes. This step is necessary to convert the sodium salt of the reagent or of the reaction by-product to free naphthol for extraction with organic solvents.
14. Extract excess of reagent and by-products of reaction by running through alcohols to absolute alcohol and then washing in absolute ether for 5 minutes.
15. Dehydrate by running through decreasing strengths of alcohols and rinse in

distilled water. Barnett recommends rapid bath of N HCl (personal communication to M.A.G.).

16. Stain for 2 minutes at room temperature in the following freshly prepared mixture (used immediately in the dark): 50 mg. tetrazo-treated diorthoanisidine in 50 ml 0.1 M Sørensen phosphate buffer, pH 7.4.

17. Wash in running tap water, 4 minutes.

18. Mount with cover glass in glycerogel.

Run control slides through steps 1-9. Immerse for 4 hours at 25° C. in 0.0015 N iodine (378 mg. per liter) containing a trace of KI at pH 3.2. Then carry slides through steps 10-15 as above.

Results. Sites of much activity show as blue color; of slight activity, as red color.

Cholesterol, Free and Esterified

Principle. The mechanism of the acetic sulfuric reaction which produces a blue-green color is unknown. Digitonin combines only with free cholesterol (unesterified 3-cis-OH groups), while the Schultz modification of the Liebermann-Burchardt test applies to both free and esterified forms (Feigin, 1956).

Method.

1. Fix overnight in cold, buffered formalin (10 per cent).

2. Cut frozen sections, mount on slides smeared with albumen.

3. Place in distilled water, 2 minutes.

4. Immerse in a 0.5 per cent solution of digitonin in 40 per cent ethanol at room temperature, 3 hours.

5. Drain and immerse in a 2.5 per cent aqueous iron-alum solution at 37° C., 2 to 4 days.

6. Simultaneously, place a duplicate section of the same material not treated as in steps 4 and 5 above, into the same solution and container in which the test section has been placed.

7. Drain fairly dry. To glacial acetic acid kept in an ice bath, add an equal volume of concentrated sulfuric acid. Cover both sections with mixture and apply coverslips.

Results. The appearance of a transient blue-green color is the characteristic positive reaction. This lasts a few minutes to hours, so

that photographs must be made if a permanent record is desired. The control slide, which omits steps 4 and 5 discloses both the free and esterified cholesterol, while the test slide discloses only free cholesterol. The difference between the sections thus indicates presence of the esters (Kent and Discker, 1955).

Arginine

Principle. A red color (as first described in the test tube by Sakaguchi) is produced when arginine reacts with oxine or with α -naphthol and hypochlorite in alkaline solution (Warren and McManus, 1951).

Method.

1. Fix in cold, buffered formalin.

2. Cut paraffin or frozen sections.

3. Carry paraffin sections through xylol to 70 per cent alcohol.

4. Place sections in 0.3 per cent solution of 8-hydroxyquinoline (oxine) in 30 per cent ethanol at room temperature, 15 minutes. (Prepare solution by adding 7 parts of water to 3 parts of 1 per cent stock solution of oxine in absolute ethanol.)

5. Place sections quickly, not allowing to drain, into alkaline hypochlorite solution, at room temperature, 60 seconds. Solution is made by adding 1 part of Clorox (1.6 N) to 9 parts .015 N KOH until the concentration of Clorox is 0.15 N.

6. Change quickly, without draining, into following alkaline urea solution: 0.15 N KOH, 10 ml.; urea, 15 Gm.; H₂O, 31 ml.; mix; tertiary butyl alcohol, 70 ml. Agitate gently for 10 seconds, then transfer to another jar of same solution for 2 minutes.

7. Transfer to pure tertiary butyl alcohol, agitate for 10 seconds, then place in another jar of same solution for 4 minutes.

8. Place in aniline (aniline oil), 3 minutes.

9. Wash in xylene, 10 seconds.

10. Mount in Permout containing aniline (One volume of 0.1 ml. aniline in 100 ml. xylene added to 4 volumes of Permout).

Reagents 4, 5 and 6 must be made fresh daily.

Results. Arginine-containing protein appears orange to red. The color is unstable and disappears in a few weeks.

DISCUSSION

It would be gratifying to be able to tabulate the specific histochemical procedures that are indicated in the study of the usual myocardial diseases. It is both unfortunate and fortunate that this is not the case: unfortunate because we do not possess enough information about the "what, when, where, how and why" of these disease conditions, and fortunate because this information is yet to be acquired since it is the autopsy pathologist, and only he, who will acquire and disseminate this necessary information. Inasmuch as there are too many differences in histochemical features to allow the easy translation of data from experiments on animal tissues to human disease, we must study human tissues.

While this new body of knowledge is yet largely to be acquired, the advancing front of histochemistry can give knowledge which is not available by present routine histologic preparations. Several of the applications of these methods are listed under the description of the technique. Some common cardiac lesions are listed, together with indicated methods.

It should be noted that limitations exist for nearly every method. The pathologist-investigator using histochemical methods would do well to have at his side *Pearse's Histochemistry*, *McManus and Mowry's Staining Methods*, or *Gomori's* or *Lillie's* books on methodology, and refer to them constantly. Details of indications, technique, and interpretation are given in these extensive treatises and cannot be covered in a chapter of this size.

Finally, the pathologist who familiarizes himself with these techniques may utilize them in research, since many of these more recent methods have not yet been applied, even in common diseases. The body of information to be acquired is large enough for trained workers in pathology to assemble it and make it available.

Applications of Histochemical Methods in Various Diseases

1. MYOCARDIAL INFARCTION

The Coronary Arteries. In experimental

necrotizing lesions of coronary arteries in the rabbit the extent of damage to the muscle is well demonstrated by the 5-nucleotidase method (McManus and Lupton, 1953). Generally, hyaline or necrotic foci are well seen in preparations with the Alcian Blue-PAS technique. The condition of the ground substance of the vessel is well shown by the same method. An analysis of the lipid deposit in the vessels requires the whole battery of Sudan IV, Sudan black and cholesterol staining methods which need supplementation by AB-PAS to give a complete picture. Blood vessels in the plaque will generally have their endothelial linings take an alkaline phosphatase stain.

The Myocardium. The changes in the myocardium produced by ischemia, such as will result from a coronary obstruction whether caused by necrotizing arteritis or coronary thrombosis, can be picked out readily at a very early stage by the methods outlined by Wachstein and Meisel (1953), by Kent and Discker (1955), and by Yokoyama and her associates (1954). It is useful to follow the progress of the disappearance of heart muscle fibers by standard histologic techniques, such as the phosphotungstic acid-hematoxylin method, while observing the changes in the ground substance with the Alcian Blue-PAS methods.

Early in the reparative process in the heart, as in every other tissue so far studied, there is a concentration of acid mucopolysaccharide, as demonstrated by strong Alcian Blue staining and by increased metachromasia. As new connective tissue fibers are laid down, and this is perhaps best seen with the classic van Gieson technique, the acid mucopolysaccharide decreases greatly, as shown by decrease in their affinity for Alcian Blue and metachromatic dyes.

Little can be added to the paper by Wachstein and Meisel (1953) regarding the enzymatic histochemical methods in myocardial infarction.

The Thrombus. The thrombus in a coronary artery frequently shows an astonishing number of ages and stages when studied with

the Alcian Blue-PAS technique. The older parts of the thrombus, as indicated sometimes by early organization and the disappearance of pigment-containing cells, shows a hyaline material which is strongly PAS-positive, while the fresher parts of the thrombus show a varying proportion of Alcian Blue-positive material. Many thrombi, when stained with hematoxylin and eosin, appear to have resulted from one episode of thrombosis but, when studied with the AB-PAS method, turn out to be crops of thrombi.

2. RHEUMATIC FEVER AND RELATED DISEASES

In a number of cases of rheumatic fever which we have studied, the ground substance of the heart shows a mucoid change demonstrable with the methods for acid mucopolysaccharides (Alcian Blue, colloidal iron positivity, metachromasia). The distribution of these changes is much more extensive than that of the Aschoff nodules and may have diagnostic value equal to actual demonstrations of Aschoff nodules. The changes are sometimes most conspicuous at the angle formed by the mitral valve and the ventricular wall, and it seems to us that this is also a favorite site for the Aschoff body.

The fibrinoid necrosis of the Aschoff body is PAS-positive and produces a striking picture with the AB-PAS stain. The older studies of Altschuler and Angevine (1943) describe the metachromatic staining of the fibrinoid degeneration of connective tissue and also indicate some limitations of interpretation.

With the onset of healing and fibrosis in the Aschoff nodules, acid mucopolysaccharides begin to appear in greater concentrations in the PAS-positive fibrinoid degeneration and healing proceeds much as in myocardial infarction. The cells of the Aschoff body are quite strongly positive with the method for 5-nucleotidase, as determined in limited unpublished studies of Lupton and McManus.

With the routine stains of hematoxylin and eosin, the muscle fibers in the first attack of rheumatic fever may appear normal, or at most, only slightly hyalinized, in relationship to the early Aschoff body. However, with the PAS method, these cells present an ab-

normal accumulation of glycogen, suggesting the early metabolic damage which will later resolve, with loss of muscle fibers adjacent to the Aschoff nodule. We have found no histochemical features that would support the suggestion that the cells of the Aschoff body originate in cardiac muscle.

Enzymatic studies in rheumatic fever and in the rheumatic group of diseases have not yet been carried out to demonstrate functional abnormalities of the myocardial fibers. The demonstration of such enzymes would represent a considerable contribution to the functional pathology of the heart.

3. MISCELLANEOUS LESIONS

Infectious agents in general have a better chance of being demonstrated by the classic bacterial stains, such as the Brown and Brenn stain or the acid-fast methods, with the exception of fungi which are best seen with the Alcian Blue-PAS or Ritter and Oleson methods. Dr. Robert Mowry has pointed out that capsules of pneumococci, streptococci and staphylococci are well shown with Alcian Blue and he recommends the Alcian Blue-Feulgen method.

Derangements of the connective tissue structure within the heart, as a result of active or previous disease, are generally well shown by the AB-PAS methods. It is possible also to obtain some evidence of the duration of the process since early lesions generally have more acid mucopolysaccharide than older ones, just as in the case of myocardial infarction.

A conspicuous exception to this rule is the condition of endocardial fibro-elastosis in which the mucoid material is frequently more conspicuous with either the Alcian Blue, Ritter and Oleson, or metachromatic methods than is the elastic tissue or the fibrous tissue with appropriate stains. The condition should probably be called mucoid fibroelastosis or some other more euphonious term which would emphasize the great concentration of mucoid material or acid mucopolysaccharides in the lesion. This association of acid mucopolysaccharides and elastic tissue has been stressed by Rinehart (1954) in relation to

the vessels, but to our knowledge has not been emphasized in endocardial fibro-elastosis.

The logical method for the study of the conduction system is a histochemical one to show the specific fibers. Carbonell (1956) has indicated that some cases of bundle block are not associated with conspicuous changes in the enzymatic activity, as shown with the pentadecanoyl substrate.

Amyloidosis of the myocardium is demonstrated about as well with the Alcian Blue-PAS method as by the older techniques, including that of King. The amyloid forms a PAS-positive material ringing the muscle fiber

and separating it from the acid mucopolysaccharides of the perimysium.

There is no really satisfactory and trustworthy method for the demonstration of hemoglobin either in erythrocytes or in heart muscle. Generally, the classic staining methods, and notably those utilizing alizarin red, will be found most satisfactory for hemoglobin. However, the breakdown products of hemoglobin, particularly hemosiderin, are well shown by the Perls iron stain, producing a striking picture when counterstained with the PAS method and with some nuclear stain added, such as hematoxylin.

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